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THE SAFETY OF INTRAVASCULAR CARBON DIOXIDE AND ITS USE FOR ROENTGENOLOGIC VISUALIZATION OF INTRACARDIAC STRUCTURES *

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THE injection of air into body cavities or tissues is a method that has been used for diagnostic purposes (e.g., perirenal insufflation, Rubin's test, etc.) and also for therapy (e.g., pneumoperitoneum, pneumothorax, etc.). Though these technics have been considered to have real value, each has been fraught with the risk of serious or even fatal accidents from air embolism.[1, 2, 3] Some accidents have been reported in the literature, but we have learned about a host of others only through personal communication. The frequency with which air embolism has been observed has varied with different procedures, but has been highest, undoubtedly, in connection with perirenal insufflation, despite the greatest care in technic. The truth of this has become so well known that there has been a general abandonment of the procedure in all medical centers. As a substitute, the presacral technic has attained considerable popularity and has been successful in providing excellent visualization of perirenal structures. However, it has not obviated the danger of air embolism, as is becoming increasingly apparent from the number of accidents being reported.[4] Nor is there safety in the substitution of oxygen for air

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(as confidently asserted by many authors), since the solubility of oxygen in plasma is little different from that of air, and the mortality rate in animals is almost identical when equivalent doses are injected intravenously.

Studies carried out by us over a period of years have led us to believe that the difficulties encountered to date need not necessitate a complete abandonment of gas injection technics. We consider that the answer lies in the utilization of a gas which has sufficient solubility to avoid the dangers to be expected with air or oxygen. Carbon dioxide seems to fulfill this requirement, since it is 20 times as soluble in serum as is air or oxygen. It is of interest that gynecologists have long been using this gas for the Rubin test and no fatalities have been reported.* Our own investigations have led us to believe not only that the use of carbon dioxide will obviate the dangers of extravascular injection, but also that it may be safely used intravenously for visualization of intracardiac structures. These conclusions are based on a large series of studies in animals and a more limited study in the human.

The Safety of Injected Carbon Dioxide

A. *Systemic Vein Injection in the Experimental Animal:* We have shown that very large amounts of carbon dioxide (7.5 c.c./kg.) can be injected rapidly into the systemic veins of dogs without harmful effect.[6] With such large doses there is a very brief rise in whole blood carbon dioxide content of 5 to 10 vol.%, accompanied by a maximal decrease of 1 to 2 vol.% of oxygen concentration. There is, of course, an associated brief hyperpnea. The maximal changes in blood gas concentration are reached in from 15 to 30 seconds, and the return to normal is complete within one to two minutes. The average change in pH has been 0.008 U.

Alterations in intravascular pressures with these large carbon dioxide injections have been minimal. The right ventricular diastolic pressure does not rise significantly when the animal is in the right or left lateral position, and only very briefly (15 seconds) when it is supine. In all positions there is a rise in right ventricular systolic pressure of moderate degree, which persists for as long as from three to five minutes. A very mild systemic arterial hypotension is an accompaniment of these changes, but does not last for longer than 15 seconds in any position and is extremely brief (six seconds) with the animal on its right side.†

It should be realized that the intravenous doses of carbon dioxide used in these experiments are far beyond the amount of those that would be needed in the human for most purposes of intracardiac visualization. Amounts as small as 2 c.c./kg. have been entirely adequate for visualization of the right ventricular outflow tract.

* Nitrous oxide has also been recommended for injection technics because of its similarly high solubility.[5]

† The latter positional effect is due to the rapid delivery of the gas into the pulmonary artery as a result of the gas buoyancy principle.

The potential value of the technic for the demonstration of human pathologic lesions of the right ventricular outflow tract has been shown by the use of animals with experimentally produced pulmonary stenosis in whom it has been readily possible to visualize the stenotic area. A double-contrast technic, using small amounts of Diodrast together with carbon dioxide (2 c.c./kg.) injected simultaneously, has provided even better visualization, though the depressing effect of Diodrast on the heart has been manifest by a marked slowing of heart rate, an effect not observed when carbon dioxide is used alone.

Further studies have been carried out in a large series of animals to demonstrate the value of the technic in the demonstration of experimental pericardial effusions. These animals had a catheter inserted into the pericardial cavity. The latter and the chest wall had been tightly closed and spontaneous respiration reëstablished. This permitted the production of effusions varying in size up to the amount which resulted in tamponade (usually between 100 to 140 c.c.). Fluids of differing specific gravities were used in the experiments and it was found as would be expected, that the heart was not buoyant in fluids having specific gravities less than that of heart muscle or blood. When animals having such fluids in their pericardial sac were studied in the left lateral position by intravenous carbon dioxide injections of from 15 to 50 c.c., the fluid surrounding the right atrial wall could be demonstrated readily with a horizontal x-ray beam. This was possible since the gas bubble was located in the right atrial cavity for a sufficient period of time to show a very marked thickening of the shadow usually cast by the combined right atrial wall and its pericardial coat. When the horizontal x-ray beam was projected through the right atrial area on an angle of 45° from the long axis of the body, interference from the shadow of the right ventricular outflow tract was eliminated. Thus the experimental work demonstrated the value of the carbon dioxide technic in the diagnosis of pericardial fluid or thickening.

B. *Left Ventricular and Systemic Arterial Injection in the Experimental Animal:* To prove the safety of any gas to be injected intravenously, it must be demonstrated that the entire amount could be tolerated if shunted from the right to the left heart through a septal defect. This demonstration is particularly necessary since it has been proved beyond doubt that the dangerous gases (air, oxygen, nitrogen) are far more lethal in the left than in the right heart. Extremely small doses of air injected into the left ventricle or aortic root are likely to result in fatality due to embolic obstruction of coronary or cerebral arteries.[2]

We have therefore injected large amounts (7.5 c.c./kg.) of carbon dioxide into the left heart and systemic arteries of dogs. The sites for these injections were (1) the left ventricle, (2) the root of the aorta adjacent to the coronary orifices, and (3) the carotid artery distal to a ligature. In each instance the procedure was extremely well tolerated. The changes in pres-

sures, respiration and electrocardiogram were minimal and brief. When the injection was into the body of the left ventricle there was noted the persistence of a small bubble of gas above the level of the left ventricular outflow tract for some time after the injection. Such a bubble, when aspirated, was found to contain up to 20% oxygen (diffusion into the carbon dioxide prior to its total absorption). No symptoms have been associated with this, and the bubble has gradually disappeared over a period of 30 minutes. It is possible, of course, that displacement of this residual gas into the left ventricular outflow tract could produce embolic effects. It is necessary to emphasize again, however, that the conditions established in these experiments are extreme ones, the dosage being far greater than any we would expect to inject into any part of the human circulation for any purpose.

Visualization of Heart Structures

A. *In the Experimental Animal:* The experiments described have demonstrated the safety of carbon dioxide when injected directly into the veins of animals. The inference is drawn that the use of this gas in the human is safe whenever it is injected into tissues or body cavities for radiography, even if the injection is made inadvertently directly or indirectly into a vascular channel. From this comes the suggestion that visualization of the cardiovascular structures themselves, as has been accomplished experimentally with air,[7] might safely be achieved by use of carbon dioxide either as a substitute for Diodrast or accompanying it as a double-contrast technic.

Toward this end we have used injections of varying amounts (2.0 to 7.5 c.c./kg.) of carbon dioxide into different parts of the circulation of the dog, visualizing the structures thus outlined by means of a Phillips Image Amplifier, low x-ray intensity, and a standard 16 mm. moving picture camera. The film recording is made at 64 frames per second, so that when viewed at the standard speed of 16 frames per second a slow-motion effect is provided. Standard moving picture film has been used. The results have been as follows:

1. Injections of 7.5 c.c./kg. into systemic femoral veins: The inferior vena cava, right atrium and right ventricle have been readily visualized. Their movements during the different phases of the cardiac cycle have been well recorded, as have been the movements of the pulmonary valve leaflets.

2. Injections of 2 c.c./kg. into systemic veins: This smaller dose has made possible selective visualization of the right ventricular outflow tract and dynamic visualization of the pulmonary valve. Proper positioning of the animal has been necessary so that the x-ray beam is at right angles to the plane of the valve.

3. Injections of 7.5 c.c./kg. into the left ventricle: This has made possible visualization of the cavity of the left ventricle, the left ventricular outflow tract and the movements of the aortic leaflets. Some regurgitation into

the left atrium and pulmonary veins usually occurs, so that these structures are also outlined. On one occasion the shunting of gas into the right atrium has been observed in an animal found subsequently to have a small interatrial septal defect. Gas leaving the left ventricle has been seen within the coronary arteries, and it is to be noted that this has had no demonstrable effects (in marked contrast to the devastating consequences of coronary *air* embolism [3]).

B. *In the Human:* We have proceeded with caution to extend the technics used in the animal to the study of humans, despite the evident safety of large doses of carbon dioxide in the former. The first experiments were performed in two anencephalic infants who had no known defect of the cardiovascular system. Doses approaching those used in animals were employed, i.e., 5.0 c.c./kg. injected rapidly. These injections were well tolerated in the supine position, with only transient apnea. In one infant the injection was repeated within a few minutes with no difficulty. Radiographs showed the right heart chambers to be briefly and clearly outlined by the gas. These experiments have been previously reported.[8]

The excellent tolerance exhibited by the infants for large doses then seemed to permit the extension of the technic to adults with cardiovascular disease, using smaller doses (0.5 to 2.0 c.c./kg.) for selective visualization of the right ventricular outflow tract. For these studies patients were chosen who had no known defect of the septum, though the evidence from animals would indicate the safety of the procedure even though shunting of the gas to the left ventricle might take place. To date, no cases of cyanotic congenital heart disease have been selected for the procedure.

Experiments have been carried out in five patients with rheumatic heart disease with mitral stenosis, ranging in age from 37 to 53 years, and with doses of 30, 50, 50, 75 and 100 c.c., respectively. Another patient who had coarctation of the aorta was given a 100 c.c. injection. Roentgen studies were made with the patient in the supine position and the beam directed horizontally in approximately the plane of the pulmonic valve leaflets. With the 100 c.c. dose, successful visualization of the right ventricular outflow tract and pulmonary valve was obtained (figure 1). The smaller doses were only partially successful. It seems probable that further study of projection technics will lead to better results.

Pericardial Disease: During the course of studies of the human heart it became evident that the carbon dioxide technic might have great value in the diagnosis of pericardial disease, and this impression was supported by the animal work referred to previously. Injections were therefore made into a group of patients suspected of having such disease. Altogether, 14 experiments were carried out in seven individuals. The patient was placed in the left lateral position and the x-ray beam was directed horizontally. In each experiment 50 c.c. of carbon dioxide were injected rapidly intravenously, and it was invariably possible to demonstrate readily a fluid level within the

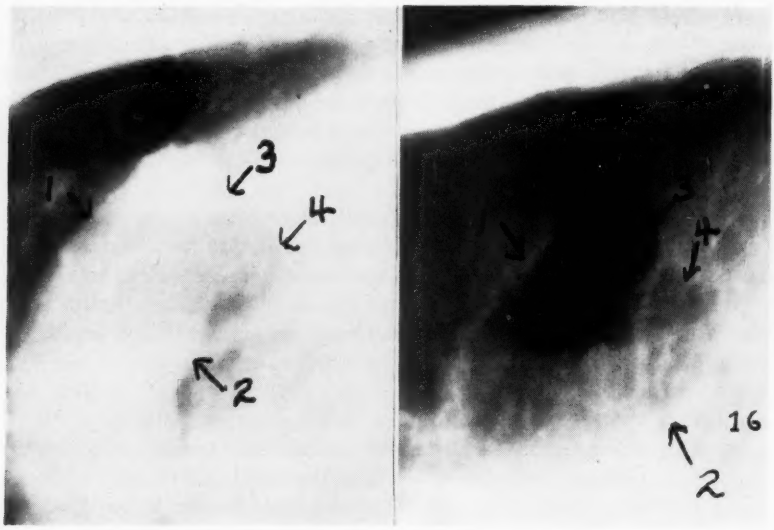

FIG. 1. Comparison of two types of angiocardiography for demonstration of right ventricular outflow tract and pulmonary artery. Patient with coarctation of aorta. A. Urokon angiocardiography. B. Carbon dioxide (100 c.c.) angiocardiography. In both A and B the figures 1 and 2 represent the walls of the pulmonary artery, and 3 and 4 designate the pulmonary valve leaflets.

right atrium. The gas persisted within that chamber for a few minutes, in most instances, and to as long as 20 minutes in one case. There were no symptoms whatsoever related to the injection.

In two of the seven patients suspected of having pericardial disease, an effusion was diagnosed. One of these, a patient with the nephrotic syndrome, had a moderate effusion, and the other, a case with myxedema, had a large one (figure 2). In the former the effusion was seen to be larger toward the diaphragmatic surface of the heart than toward the base. This phenomenon has been noted also in animal experiments. Angiocardiography (Urokon) had been unsuccessful in this case. A third patient was shown to have pleuropericardial thickening secondary to and following the drainage of a right-sided empyema. A fourth patient was known to have had calcific constricting pericardial disease prior to the injection. The experiment demonstrated a rigidity and flattening of the right atrial wall (figure 3). The diagnosis in this case was confirmed by surgery. In the three remaining cases studied for possible pericardial disease no evidence of fluid or thickening of the pericardium was found, and it was concluded that the large heart shadow was the result of cardiac dilatation alone. An example of one of these cases is shown in figure 4.

C. *Factors of Importance in Injection Technic:* We should like to emphasize certain factors in injection technic which we feel to be of great im-

portance for safe injection of carbon dioxide gas into the veins of patients. It should be obvious, first of all, that the gas to be injected must be *pure* carbon dioxide. The mixtures of oxygen and carbon dioxide available under the misleading term "hospital carbon dioxide" would have all the hazards of gas embolism in proportion to the amount of oxygen contained in them.

It has been our practice also to make certain that the 50 or 100 c.c. syringe used for the injection, together with the three-way stopcock and the needle attached to it, forms an air-tight unit. The syringe is filled twice with carbon dioxide and this gas expelled before the final filling used for the injection. It is probably true that the amount of contamination of the carbon dioxide that could occur if these precautions were not followed would be too small to be significant, but we do not feel that it is wise to take the slightest chance. The injection may be made into any readily available systemic vein, with or without a previously established intravenous fluid drip. The usual sterile technic precautions are used for the injection apparatus, though no special treatment of the gas itself has been needed. The

FIG. 2. Pericardial effusion in patient with myxedema demonstrated by carbon dioxide injection (50 c.c.). Patient on left side. Horizontal x-ray beam. Note gas bubble and fluid level within right atrium and separated by a considerable distance from the right heart border.

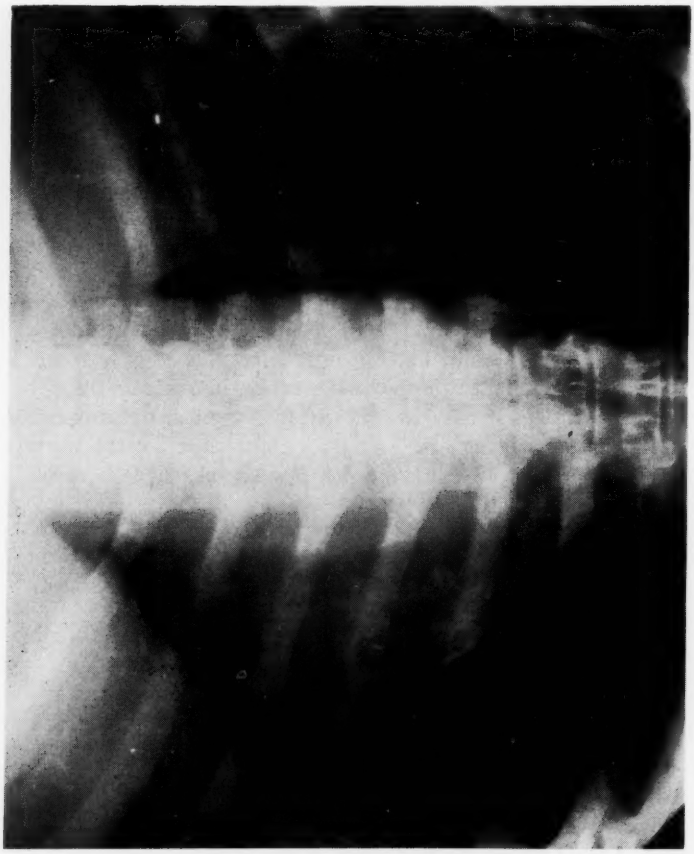

FIG. 3. Carbon dioxide angiocardiography in patient with chronic constrictive pericarditis. Note gas bubble and fluid level within right atrium and the flattening of the right atrial wall. The deformity of this wall was also demonstrated by Urokon angiocardiography. Note calcification along left heart border.

total quantity of carbon dioxide to be given is injected as rapidly as possible to obtain maximal concentration for a brief period within the right heart. At the present time we do not use injections larger than 2.0 c.c./kg. body weight, but it is quite possible that larger amounts will eventually be employed, particularly in view of the experience we have reported with anencephalic infants, and the much larger amounts tolerated well by animals.

DISCUSSION

The experiments which have been described in this paper provide what we believe to be conclusive evidence for the safety of intravenous carbon

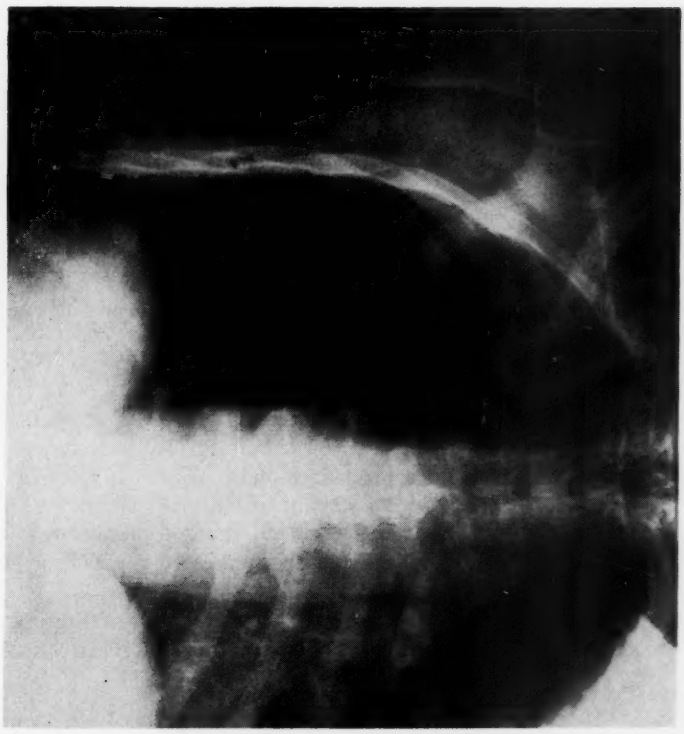

FIG. 4. Patient with large heart shadow suspected of having pericardial effusion clinically. Carbon dioxide study (50 c.c.) did not confirm this. Note that there is no widening of the right atrial wall shadow, as demonstrated by contrast with the gas bubble within the cavity of the chamber. The curve of the shadow cast by the right atrial wall is the one normally seen and is in contrast to that seen in figure 3.

dioxide. This safety is undoubtedly related to the high degree of solubility of this gas in serum, and is in marked contrast to the danger and low solubility of air or oxygen. The latter gases involve a very real risk of fatal gas embolism when injected into the body tissues, even in the supposedly safe presacral technic. It would appear, therefore, that carbon dioxide should be the gas of choice for any such diagnostic injection. The more rapid absorption of this gas will require accurate timing of x-ray exposures, but should provide a contrast with the tissues of the body that is satisfactory for most purposes.

The use of carbon dioxide injected directly into the vascular system for demonstration of intracardiac structures is a new technic which seems warranted in selected cases on the basis of the animal and human experiments which have been carried out to date. Its most practical use so far has been as a supplement to other diagnostic procedures in the diagnosis of pericardial

disease, particularly that associated with effusion. For this purpose small doses (50 c.c. for the average adult) are adequate and should prove to be a simpler means than angiocardiography for distinguishing between large heart shadows due to dilatation and those due to effusion. Experience with one case of calcified constricting pericardium leads to the suggestion that a right atrial wall shadow which is rigid and which has lost its characteristically rounded contour may be an important sign of this disease.

Our preliminary studies relating to the right ventricular outflow tract suggest that larger doses (about 100 c.c.) may prove to be of value in the study of this structure and of the pulmonary valve. The cases in which we have used the technic to date have not had disease in this region, but experimental work in the animal indicates that stenotic lesions can be demonstrated. Obviously, more work needs to be done in the human. The risk of gas passing through a septal defect to the left ventricle seems to be of little importance in view of the experiments reported above, in which large doses have been injected directly, without untoward effect, into the left ventricular cavity, aortic root and carotid artery of animals. There is also the future possibility that direct injection into the human left ventricle may be a valuable supplement to left heart catheterization, though the residual bubble phenomenon referred to previously leads to some need for caution, despite the apparent safety in animals.

We believe that there is one important absolute contraindication to the injection of carbon dioxide for any purpose whatsoever. This concerns the patient with pulmonary emphysema or fibrosis whose excretory mechanism for carbon dioxide is impaired. In such a case a high grade of carbon dioxide narcosis might well be produced.

Summary

Large doses of *pure* carbon dioxide have been injected repeatedly intravenously and into the left heart of animals without untoward effect. Doses up to 100 c.c. have been injected intravenously into human beings, also without untoward effect.

In both animals and man injections of carbon dioxide provide a means of contrast roentgen visualization of intracardiac structures and events which is particularly effective when recorded by moving picture technic. The technic is especially useful in the diagnosis of pericardial disease, but may be found to be equally valuable for study of the right ventricular outflow tract. Stress has been placed upon the importance of using *pure* carbon dioxide gas for any human injections.

Carbon dioxide should be used as a substitute for either air or oxygen whenever injections are to be made into tissues for gas contrast roentgen technics in order to avoid the danger of serious embolism.

SUMMARIO IN INTERLINGUA

In previe studios nos ha demonstrate que aere, injicite in le systema circulatori de animales experimental, resulta in excellente roentgeno-visualisation de structuras intracardiac. Tamen, le periculos associate con tal injectiones non permitte le uso de iste technica pro objectivos diagnostic in humanos. Per consequente, nos ha effortiate nos a trovar un gas que pote esser injicite sin risco e que nonobstante servirea como medio de contrasto equivalente al aere. Ha essite trovate que pur bioxydo de carbon satisface iste requirimentos a causa de su alte grado de solubilitate in plasma (20 vices illo de aere o de oxygeno a temperaturas corporee). Iste gas pote esser injicite repetitemente in le corde sinistre o dextere de animales sin effectos adverse, mesmo in grande doses (7,5 cm³ per kg de peso corporee). Con le utilisation del amplificator de imagines de Phillips (que rende le imagine fluoroscopic 1.000 vices plus luminose), nos ha cinematographate (con apparaturas standard) le eventos cardiac que seque tal injectiones de gas. Le projection relentate del pelliculas assi obtenite esseva de grande adjuta in lor analyse. Con injectiones intravenose de bioxydo de carbon il deveniva possibile visualisar clarmente le cameras dextero-atrial e -ventricular e observar le aperir e le clauder del valvula pulmonar. Con le injection de bioxydo de carbon in le ventriculo sinistre il deveniva possibile visualisar non solmente le cavitates del ventriculo e atrio sinistre (per regurgitation del gas a in le atrio) sed etiam le aperir e clauder del valvula aortic. Le gas ha etiam essite vidite in le arterias coronari. In un serie de patientes human con morbo cardiac nos ha injicite 30 a 100 cm³ de bioxydo de carbon per via intravenose sin effectos adverse. Isto esseva specialmente utile in le diagnose de morbo pericardial—tanto de effusion pericardial como etiam de chronic pericarditis constrictive. Le methodo ha etiam providite un excellente visualisation del via de effluxo dextero-ventricular. Altere applicationes del technica va sin dubita disveloppar se in le curso del tempore.

Iste studios demonstra le securitate de injectiones intravenose de bioxydo de carbon pro objectivos de angiocardiographia a contrasto. Illos etiam monstra que bioxydo de carbon debe esser le medio de election in omne injectiones diagnostic de gas (per exemplo in insufflation presacral) a fin de evitar le catastrophes que pote occurrer con le uso de aere o oxygeno.

BIBLIOGRAPHY

1. Durant, T. M., Long, J., and Oppenheimer, M. J.: Pulmonary (venous) air embolism, Am. Heart J. **33**: 269, 1947.
2. Durant, T. M., Oppenheimer, M. J., Wester, M. R., and Long, J.: Arterial air embolism, Am. Heart J. **38**: 481, 1949.
3. Oppenheimer, M. J., Durant, T. M., and Lynch, P.: Body position in relation to venous air embolism and the associated cardiovascular-respiratory changes, Am. J. M. Sc. **225**: 362, 1953.
4. Ransom, C. L., Landes, R. R., and McLelland, R.: Air embolism following retroperitoneal pneumography: a nation-wide survey, J. Urol. **76**: 664, 1956.
5. Teschendorf, W.: On the use of quickly absorbent gases in x-ray diagnosis, Acta radiol. **36**: 297, 1951.
6. Oppenheimer, M. J., Durant, T. M., Stauffer, H. M., Stewart, G. H., Lynch, P. R., and Barrera, F.: In vivo visualization of intravascular structures with gaseous carbon dioxide: cardiovascular effects and associated changes in blood chemistry, Am. J. Physiol. **186**: 325, 1956.
7. Durant, T. M., Oppenheimer, M. J., Lynch, P. R., Ascanio, G., and Webber, D.: Body position in relation to venous air embolism: a roentgenologic study, Am. J. M. Sc. **227**: 509, 1954.
8. Stauffer, H. M., Durant, T. M., and Oppenheimer, M. J.: Gas embolism: roentgenologic considerations, including the experimental use of carbon dioxide as an intracardiac contrast material, Radiology **66**: 686, 1956.

THE VARIED CLINICAL MANIFESTATIONS OF PULMONARY EMBOLISM *

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PULMONARY embolism is a common finding at necropsy. It is nevertheless regarded in many hospitals as an unusual disorder, infrequently considered in the differential diagnosis of cardiopulmonary diseases.

The frequent failure to recognize pulmonary embolism clinically can best be explained on the basis of widely held misconceptions regarding the prevalence of this disorder and the evidence necessary for its diagnosis.

If the diagnosis is considered only when all the classic clinical and laboratory features are demonstrable, most instances of embolism will go unrecognized. Where physicians are familiar with the variety of clinical, radiologic and electrocardiographic manifestations which characterize pulmonary embolism, the frequency and importance of this disorder in modern practice become evident.

Excellent pathologic studies of embolism and infarction have been numerous,[1-3, 9] clinical investigations few.[4, 17, 20] In clinical studies, moreover, the approach has varied according to the interests of the investigators. In some, pulmonary embolism has been regarded chiefly as a cardiovascular catastrophe, and attention has been concentrated on the electrocardiographic criteria of diagnosis. In other studies, embolism has been regarded as a pulmonary disease, and attention has been confined largely to the radiologic aspects of diagnosis. No data have been reported concerning the relative frequency of the respiratory and circulatory manifestations of pulmonary embolism in general hospital practice.

As a result of growing interest in this disease at the Graduate Hospital, the diagnosis has been made with increasing frequency in recent years. During the last 18 months the entire house staff has coöperated in an effort to detect clinically instances of pulmonary embolism on all services of the hospital. The number recognized exceeded all anticipation, and provided a unique opportunity to measure the relative frequency of the various respiratory, cardiovascular, abdominal and neurologic guises which pulmonary

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embolism may assume. These observations are reported in the belief that greater familiarity with these varied manifestations and more widespread appreciation of the frequency of pulmonary embolism in modern hospital practice are essential if improved diagnosis of this important and common disease is to be achieved.

The Frequency of Pulmonary Embolism

Statistics on the occurrence of pulmonary embolism vary widely, according to whether studies are made on (1) necropsy material in hospitals, (2) necropsy material in nonhospitalized patients, or (3) on clinical material. The range of observations is shown in table 1, utilizing representative studies from well known hospitals and institutions.

The significance of emboli is often indicated by classifying them (a) as the cause of death, (b) as a contributory cause of death, and (c) as incidental. The frequency with which pulmonary embolism is detected at necropsy will be influenced by the thoroughness and interest of the pathologist, and in the routine work of an overtaxed pathologic laboratory small emboli and infarctions may be overlooked.

The degree of variation is indicated by Hampton and Castleman's observation that pulmonary embolism was detected in 9% of routine necropsies at Massachusetts General Hospital, and in 14% of a specially studied group of 400 cases.[2] The similarity of findings in the various pathologic studies included in table 1 is notable.

It will be seen in table 1 that massive embolism is observed in approximately 4% of all hospital necropsies, while contributory embolism and incidental embolism are noted in 3%. The detection of pulmonary embolism in about 10% of patients dying in general hospitals has been remarkably constant over a period of years. American studies reported in 1934,[1] 1945 [6] and 1952 [8] have each shown pulmonary embolism to be present in about 10% of cases. It should be noted, however, that Short [4] surveyed autopsy records of two English hospitals and noted a sharp rise in the frequency with which massive embolism caused death between the years 1913 to 1917 and the years 1944 to 1948. It is possible that this rise is merely the result of

Table 1

Frequency of Pulmonary Embolism Reported in Various Hospitals and Institutions

Population Studied	Method of Study	Massive Embolism, Per Cent	Other Embolism, Per Cent	Total Embolism, Per Cent
Hospital deaths[1–9]	Necropsy	1.0–7.0	3.0–5.4	6.2–14.0
Homes for indigent[10, 11]	Necropsy	6.8–14.2	11.5–16.3	23.1–25.7
Postoperative patients[4, 7, 8, 12–17]	Clinical, Necropsy	0.03–0.37	0.02–0.35	0.2–0.5
Medical patients[4, 19–22]	Clinical, Necropsy	0.12–0.5	0.32–2.0	0.6–2.5

increasing age at death, with more deaths due to degenerative disease and fewer due to infection.

Two excellent studies of necropsies performed on inmates dying in homes for the indigent demonstrate an even higher occurrence of pulmonary embolism and infarction. Both in Pittsburgh [10] and in Columbus,[11] embolism or infarcts were found in 25% of necropsies, and in approximately 10% of necropsies massive embolism was the immediate cause of death. Towbin [11] has emphasized that these observations in homes for the indigent are more typical of the population at large than are observations made on hospital patients.

Clinical estimates of the frequency of pulmonary embolism are of a much lower order of magnitude. Pulmonary embolism is more dramatic in surgical patients who might but for this catastrophe have fully recovered. For this reason, and because the period of risk in surgical patients is shorter and more easily measured, the problem of thrombo-embolism has in the past been given more study on surgical than on medical services. The frequency of postoperative embolism reported in most studies, however, is low; the average incidence of massive pulmonary embolism following surgical procedures is approximately 0.18%. The reported incidence of nonfatal postoperative embolism is little higher, averaging 0.20%.

The frequency of embolism is greater among medical patients,[4, 8] but direct comparison of ratios is misleading, since the age of medical cases is greater and their stay in the hospital usually longer. Although the reported incidence varies over a wide range, the mean embolism rate is 1.1% of all medical admissions. Approximately 0.4% represent massive emboli, fatal within minutes or hours; the remaining 0.7% represent smaller emboli which are nonfatal, or are merely contributory to death.

In another important group of patients there is a significant prevalence of embolism, but no quantitative data are available. These are the ambulatory patients who, either because of underlying disease or because of trauma, often trivial, or without known predisposing factors, develop thrombo-embolism. More than a third of our patients with pulmonary embolism were of this type, and a third of our fatal cases died of thromboembolic disease with which they had entered the hospital.

Relative Frequency of Embolism and Other Pulmonary Diseases

With the decline in frequency of infection in medicine and surgery, pulmonary embolism has increased in importance as a cause of illness and death to a degree that is not generally appreciated. Short,[4] in an excellent study of the occurrence of pulmonary embolism in a general hospital in England, made the observation that pulmonary embolism was the most common acute pulmonary disease encountered between 1947 and 1950 at the Southmead Hospital in Bristol, exceeding in prevalence lobar pneumonia, bronchogenic carcinoma and idiopathic pleurisy with effusion. A review of records

TABLE 2

Frequency of Diagnosis of Certain Pulmonary Diseases
Graduate Hospital, 1942–1957

Years	Diagnosis	Annual Rate
1944–50	Pulmonary embolism	5.6
1951–52	Pulmonary embolism	12.0
1955–57	Bronchogenic carcinoma	30.0
1955–57	Pneumonia	33.3
1955–57	Pulmonary embolism	60.0

at the Graduate Hospital in 1952, however, indicated that despite special interest in the diagnosis of pulmonary embolism, pneumonia and bronchogenic carcinoma far outnumbered pulmonary embolism (table 2).

In 1955 a study was instituted at the Graduate Hospital to ascertain the value of serum transaminase determinations as an aid to the differentiation of pulmonary embolism and myocardial infarction. It was quickly evident that the frequency of pulmonary embolism was far greater than was anticipated, and a total of 90 cases was detected in the next 18 months, representing an annual rate of 60. Comparison with the cases of pneumonia and bronchogenic carcinoma admitted to Graduate Hospital during the same 18-month interval demonstrates that pulmonary embolism is indeed the most common pulmonary disorder encountered in this hospital.

The very sharp rise in frequency recorded at Graduate Hospital may in small measure reflect an actual increase in prevalence in an aging hospital population, but we believe the increase to be principally the result of better diagnosis. The fact that resident physicians and surgeons as well as the radiologic staff have become alert to the frequency of pulmonary embolism is in our opinion the major factor in the apparent rise.

PULMONARY EMBOLISM AT GRADUATE HOSPITAL

Clinical Material: The diagnosis of pulmonary embolism was made in 90 patients at the Graduate Hospital in the 18-month period between August 1, 1955, and January 31, 1957. This includes seven patients in whom the diagnosis was not suspected antemortem, and 83 patients in whom the diagnosis was made on clinical evidence. The majority of the patients were examined and diagnosed by one or both of the authors. During the period of this study there were 10,130 adult admissions to the 350-bed Graduate Hospital, comprising 5,912 surgical and 4,218 medical admissions. There is no obstetrical department. There were a total of 9,088 surgical operations, including those on children, and a total of 221 necropsies.

It is believed that through the coöperation of the entire resident staff we were notified of all patients in whom pulmonary embolism was demonstrated or suspected. Since many of the patients were private patients, and since in many instances the diagnosis was not made at the time of occurrence of the

embolic episode but was made retrospectively after all the evidence was obtained, clinical and laboratory data are not complete in all cases.

Diagnostic Criteria: The clinical diagnosis of pulmonary embolism was based on generally accepted criteria,[2, 16, 18] i.e., by finding compatible symptoms and signs and at least one of the following: (1) evidence of thrombophlebitis of the deep veins, (2) characteristic findings in the roentgenogram of the chest, and (3) characteristic electrocardiographic abnormalities. Since the diagnosis of pulmonary embolism cannot be proved by any laboratory test, but remains essentially a clinical one, it is difficult to convince the skeptical of the diagnosis. Those who demand absolute proof before the diagnosis is accepted and treatment instituted may only too often be provided with the only absolute proof, namely, the autopsy. Since a healthy amount of skepticism is not alien to the authors, the accuracy of our clinical diagnoses has been checked by analyzing the necropsy findings of patients in whom an antemortem diagnosis of pulmonary embolism had been made by the authors. There were 10 such patients. Pulmonary infarcts were found by the pathologist in seven cases. In two cases autopsied several weeks after the embolism, findings were equivocal. In one case, most typical clinically, the embolism could not be demonstrated at necropsy; the embolus may have disintegrated and liquefied, or the diagnosis may have been in error. On the whole, these findings indicate that our clinical diagnoses were soundly based.

Incidence of Embolism: The 90 cases represent an attack rate of 0.09% among the 10,130 adults admitted during this interval. The rate among admissions to the medical service was 1.2%, and among those admitted to surgical services, 0.6%.

The rate noted among medical patients is higher than that observed in the few comparable American studies (table 1), but is not so high as the rate of 2.5% reported by Short.[4] The rate of 0.6 per hundred surgical admissions is comparable to that generally observed in such studies.

Thirty-three instances of embolism occurred after surgery; four patients died of massive embolism, giving a rate of postoperative fatal embolism of 0.04%. This is a much lower incidence than that reported in most Ameri-

TABLE 3

Mortality Among 90 Patients with Pulmonary Embolism
Graduate Hospital, 1955–1957

Outcome	Number of Patients	Per Cent
Recovered	69	76.6
Died	21	23.4
Number with necropsy	17	
Embolism occluding major vessel responsible for death	9	
Embolism occluding moderate sized vessel, contributing to death	7	
Embolism, incidental to other causes of death	5	

can hospitals, and approaches the rate of 0.03% reported by Bauer [12] in Sweden. The attack rate of nonfatal embolism in postoperative patients at Graduate Hospital was 0.32%; the ratio of diagnoses of nonfatal to fatal embolism was 8:1.

Nine instances of massive embolism were encountered in the 221 necropsies performed during this period. This represents a frequency of 4.1% of autopsied cases. In addition to two postoperative deaths, two occurred in patients admitted to the hospital with phlebitis, one occurred in a patient awaiting urologic surgery, and four represented the terminal event in patients with carcinoma. Eight other patients had moderate or small infarcts. The total with evidence of embolism or infarction at necropsy was 7.7%.

Of the 90 patients with pulmonary embolism, 69 (76.6%) recovered from their illnesses and 21 (23.4%) died within the period of study. The significance of pulmonary embolism in the causation of death is indicated in table 3. When these 21 cases are analyzed in detail, it is considered clinically that pulmonary embolism was merely contributory to the deaths of seven patients, and was an incidental finding in five others. In nine instances death is attributed entirely to embolism, since no other cause of death was evident. Four were postoperative patients in whom thrombo-embolic disease was not suspected, and who were not receiving treatment for thrombo-embolism. Two patients admitted to the hospital for treatment of thrombophlebitis of the legs died within 30 minutes and six hours of admission, respectively, before effective treatment could be instituted. Another patient admitted with thrombophlebitis died within 48 hours after admission despite vigorous anticoagulant treatment. One was a patient awaiting urologic surgery, and one was convalescent from the nephrotic syndrome. The seven cases in which pulmonary embolism was classified as a contributory cause of death include three with extensive myocardial infarction complicated by pulmonary embolism, one with advanced rheumatic heart disease, one with ascending polyneuritis, one with severe hepatitis, and one with extensive body burns. The frequency with which pulmonary embolism caused or contributed to death in this series of patients again emphasizes the importance of thrombo-embolic disease and the need for further study of the diagnosis and treatment of this dangerous condition.

Factors Predisposing to Thrombo-embolism

In an effort to improve the accuracy of detection of pulmonary embolism, a detailed analysis will be presented of the syndromes, symptoms, signs, and radiographic, electrocardiographic and laboratory findings in this series of 90 cases. First, however, it will be useful to review certain epidemiologic observations in these patients. Knowledge of the presence of predisposing factors is in many instances of prime importance in leading to the suspicion of pulmonary embolism.

Pulmonary embolism was preceded by surgery in slightly more than a third of cases at Graduate Hospital (table 4). Trauma resulting in skeletal-muscular injury appeared to be a factor in six instances. Twenty per cent of patients with embolism had been hospitalized with medical illnesses. More than a third of the patients suffered pulmonary embolism outside of the hospital, and it was symptoms of embolism or those of heart failure precipitated by embolism which led to hospitalization.

Mayo Clinic studies [17] showed that postoperative embolism was somewhat more common in the presence of obesity, anemia, cardiac disease, varicose veins, previous thrombophlebitis, severe infections and carcinoma. In a third of their patients, however, none of these predisposing factors was present. Embolism was most common from the eighth to the fourteenth day following surgery, but a quarter of cases occurred in the first week and an equal number after the second week. The risk of embolism was proportional to the severity of the surgical procedure; the ratio was lowest following surgery for hernia and chronic appendicitis, and highest after gastrectomy, cholecystectomy, splenectomy and hysterectomy.

Thromboplebitis may originate at the site of contusions and fractures. A common type of traumatic phlebitis encountered in hospital practice is that due to repeated venipuncture, to prolonged insertion of polythene tubes in veins, and to the intravenous administration of many commonly used diagnostic and therapeutic agents, such as hypertonic glucose and saline solutions, bromsulfalein and mercurial diuretics.

Among the medical diseases which predispose to thrombo-embolism are heart disease, polycythemia vera, anemia and other blood dyscrasias, and carcinoma. The notable frequency of thrombosis in patients with congestive failure or paralyses is indicative of the importance of stasis. Thrombosis and embolism, especially when recurrent despite anticoagulant therapy, have been reported to be an early sign of occult visceral carcinoma. However, a recent study by Anlyan and associates [23] casts doubt on this observation, and suggests that the alleged association has been based on impressions derived from isolated cases rather than on adequate statistical observations. Although it is possible that there is a more than coincidental relationship, in our experience it has not been rewarding to institute extensive diagnostic procedures in search of malignancy solely because of thrombophlebitis.

TABLE 4

Predisposing Influences in Patients with Pulmonary Embolism
Graduate Hospital, 1955–1957

Predisposing Factor	Number of Patients	Per Cent
Surgery	33	36.7
Trauma	6	6.7
Medical illness	18	19.9
Patients admitted with pulmonary embolism	33	36.7

TABLE 5

Age Distribution of Patients with Pulmonary Embolism Compared to Adult Population Graduate Hospital, 1955–1957

Age Group	Patients with Embolism	Percentage of Total	Distribution of Sample of Hospital Population, Per Cent
21–30	3	3.3	9.5
31–40	11	12.2	16.5
41–50	13	14.5	18.4
51–60	25	27.7	18.4
61–70	22	24.5	23.9
71–80	13	14.5	10.3
81–90	3	3.3	2.9
	90	100.0	100.0

The importance of age as a factor favoring the development of thromboembolism has been repeatedly emphasized,[11, 17] and it has been noted that 85% of cases of pulmonary embolism occur in persons over the age of 40. It will be seen in table 5, however, that 74% of all Graduate Hospital admissions exceeded that age. The rise in incidence of pulmonary embolism with age has perhaps been exaggerated. In any event, pulmonary embolism is not uncommon in persons under 40, and one should be as alert to the possibility of embolism in the young as in the aged.

THE VARIETY OF CLINICAL MANIFESTATIONS

The wide variety of manifestations of pulmonary embolism is not generally appreciated. The typical clinical picture of chest pain in a patient with frank venous thrombosis occurred in but 20% of our cases. Less well known are other syndromes, with which every internist should be acquainted, for some occur with considerable frequency (table 6).

Predominantly respiratory syndromes were most common. These were encountered in 39 patients, 43.3% of the total number with pulmonary embolism. The resemblance to pneumonia is often close, both clinically and on roentgenologic study. Since pneumonia is almost invariably preceded by upper respiratory tract infection, the absence of such illness should lead to suspicion of embolism. Recurrent episodes involving one lung and then the other are relatively infrequently due to pneumonia; this pattern is characteristic of embolism.

Pulmonary embolism is frequently the cause of "dry" pleurisy, i.e., a pleural friction rub with negative chest roentgenogram. This should not be attributed to pneumonia if the chest x-ray is negative, and tuberculosis is rarely if ever manifested in this fashion. Pleurodynia due to Coxsackie virus infection also requires consideration, especially if multiple cases of chest pain are encountered.

Pleural effusion of considerable size may be produced by infarcts. The

TABLE 6

Frequency of Pulmonary, Cardiac, Abdominal and Neurologic Syndromes in Patients with Pulmonary Embolism

Graduate Hospital, 1955–1957

	Number of Patients, Per Cent
Manifestations suggestive of	
Pneumonia	18
Dry pleurisy	10
Pleurisy with effusion	7
Lung abscess	2
Tuberculosis	1
Lung cancer	1
Pulmonary syndromes	39 (43.3%)
Myocardial infarction	22
Coronary insufficiency	4
Postinfarction syndrome	3
Congestive failure	3
Cor pulmonale	1
Cardiac syndromes	33 (36.7%)
Acute surgical abdomen	2
Subdiaphragmatic abscess	2
Primary hepatic disease	2
Abdominal syndromes	6 (6.7%)
Syncope	2
Convulsions	1
Hemiplegia	1
Neurologic syndromes	4 (4.4%)
Other manifestations	8 (8.9%)

cell count and cytologic study usually show numerous red blood cells, and approximately equal numbers of granulocytes and lymphocytes. The effusion is grossly bloody in half of the cases, usually in those with congestive failure. Effusion may continue for several weeks and lead to considerable concern over the possibility of tuberculosis or neoplasm. If in such cases biopsies of the parietal pleura reveal neither tuberculosis nor neoplasm, embolism is a likely cause.

Pulmonary tuberculosis may also be simulated by infarction. One patient thought to have tuberculosis because of hemoptysis, a history of contact with a tuberculous wife, and a right subclavicular infiltration, proved to have embolism originating in an axillary vein.

Infarcts may assume a rounded form roentgenologically, and whether symptoms of chest pain and hemoptysis are present or absent, there may be serious concern over pulmonary neoplasm. Thoracotomy has not infrequently been performed because of such findings, and merely an organizing infarct found in the resected specimen.[24]

The usual pulmonary infarct is uninfected, and secondary infection is uncommon. Lung abscess occasionally develops, however, and since this

type of abscess usually extends to the pleura, empyema may result.[25, 26] Such pyogenic complications are quite rare at present, perhaps because of the widespread use of antibiotics. It is possible that embolism may have been more commonly responsible than was realized for the abscesses and empyemas of the era before chemotherapy was available.

Cardiac Syndromes: Symptoms and signs suggestive of cardiac disease were the dominant manifestation in 33 patients. The association of congestive failure and embolism is reciprocal. Heart failure and the resulting immobilization of the patient are important predisposing influences toward venous thrombosis; and pulmonary embolism is commonly responsible either for sudden precipitation of heart failure or for its persistence in spite of treatment.

Acute myocardial infarction was the disorder most commonly confused with pulmonary embolism in the patients studied at the Graduate Hospital. Again, these disorders are intimately related.

Not only may the two resemble each other, but pulmonary embolism is also not infrequently a sequel of myocardial infarction. On the other hand, severe pulmonary embolism may be complicated, as a consequence of pulmonary hypertension and systemic hypotension, by subendocardial myocardial infarction. Electrocardiographic study may not suffice to distinguish these various complications, and determination of serum transaminase levels may be especially useful in these circumstances.

Angina Pectoris and Coronary Insufficiency: These diagnoses are often mistakenly applied to instances of recurrent chest or precordial pain which occur in ambulatory patients and which prove to be due to multiple small emboli. These patients usually have mild chronic thrombophlebitis, and exhibit only minimal roentgenologic and electrocardiographic changes.

Chronic Cor Pulmonale: Patients may have recurrent showers of small emboli with slight or no pain, with eventual obstruction of enough of the pulmonary arterial bed to result in pulmonary hypertension. Owen and his associates [27] reported 12 cases of chronic cor pulmonale due to insidious and unrecognized emboli.

Neurologic Syndromes

Syncope: Transient loss of consciousness is a not infrequent accompaniment of hypotension, chest pain and dyspnea in severe embolism. Syncope occasionally occurs as the result of embolism in the absence of these other symptoms. Two patients in the present series exhibited syncope without pain, and Hussey and Katz [25] have recorded a fatal case of this type.

Cerebral Vascular Insufficiency: Hemiplegia and convulsive phenomena may result from diminished cardiac output following pulmonary embolism, especially when this occurs in elderly patients with advanced cerebral arteriosclerosis. Two patients in this study represented instances of this syndrome.

Abdominal Syndromes

Severe upper abdominal pain with marked muscle guarding simulating true rigidity may be a manifestation of pulmonary infarction, and intra-abdominal disease was suspected on admission in six patients. The abdominal symptoms presumably result from referred pain due to irritation of the lateral portion of the right leaf of the diaphragm, or to distention of the liver capsule in patients with acute congestive failure due to pulmonary embolism. A diagnosis of cholecystitis is occasionally made, and laparotomy has been performed in such circumstances; the cause for the symptoms and normal abdominal findings may not be discovered until postoperative chest x-ray examination discloses evidence of infarction.

Symptoms and Signs

Pulmonary embolism should be included among the diagnostic possibilities whenever one of the syndromes enumerated in table 5 is encountered. Following is a detailed consideration of the individual symptoms, signs and laboratory features which were encountered in the 90 patients under study. Familiarity with these manifestations should greatly increase the accuracy of recognition of pulmonary embolism and infarction.

Not all of the classic symptoms, signs or laboratory findings occur in all patients with pulmonary embolism, and no single finding constitutes a sine qua non for the diagnosis of pulmonary embolism (tables 7 and 8). Hemoptysis and pleural friction rub are the two clinical findings which are usually regarded as most characteristic of pulmonary embolism, and which many physicians still consider indispensable to the diagnosis; both were relatively uncommon in this series (28.9 and 24.4%, respectively), and in Short's series ("less than 40" and 22.6%, respectively). Far more common were nonspecific symptoms and signs such as fever (78.9%), dyspnea (46.7%), pleuritic chest pains (56.7%), pulmonary râles (63.3%), tachycardia (58.9%), and tachypnea (44.4%). Obviously many of these manifestations are, in part at least, the result of such underlying diseases as congestive heart failure, trauma and infection. Nevertheless, these figures indicate the relative frequency of the various manifestations of pulmonary embolism encountered in hospital practice.

Fever, usually low grade, was observed in 78.9% of patients, and persisted despite the use of antibiotics in many cases. A response to anticoagulant therapy was often noted. Nine patients had temperatures of 103° F. and above; five of these went on to a fatal termination.

Anginal pain, sometimes prolonged—that is, precordial pain not related to respiration, presumably reflecting underlying coronary artery disease—was described in 27.8% of patients. In most instances of anginal pain, pleuritic pains were also noted. It is important that the history of both types of pain be elicited, since the pleuritic pains which may be overshadowed

TABLE 7

Frequency of Symptoms in 90 Patients with Pulmonary Embolism
Graduate Hospital, 1955–1957

Symptom	Number with Symptom	Per Cent
Chest pain	65	72.2
Pleuritic	51	56.7
Anginal	25	27.8
Dyspnea	42	46.7
Abdominal pain	11	12.2
Syncope without pain	2	2.2

by the more severe precordial oppression may provide the lead to the correct diagnosis. The pleuritic pain of embolism, it should be noted, is often agonizingly severe, especially in younger and more sthenic patients. The pain as a rule is more severe than the pain experienced in pneumonia.

Friction rubs are often faint, of short duration, and localized to small areas. Hence frequent and careful auscultation of the chest is required to elicit this important sign. Râles are frequently described, usually localized to the area of pleuritic pain. In most instances these fine râles are actually of pleural origin, but they are often misinterpreted as indicating congestive failure or pneumonitis.

Hypotension following pulmonary embolism was encountered in a total of 25 patients. Two patients had no pain, and syncope was the dominant symptom.

Congestive heart failure was present in a smaller percentage of our patients (25.6%) than reported in many other series.[4, 20] That congestive heart failure predisposes to pulmonary embolism and, in turn, may be precipitated by or made refractory to routine measures by the superimposition of pulmonary emboli has been stressed by others.[4]

Tachycardia and tachypnea out of proportion to the patient's fever and pulmonary congestion should always suggest pulmonary embolism. However, it should be emphasized that tachycardia and tachypnea may be absent:

TABLE 8

Frequency of Signs in 90 Patients with Pulmonary Embolism
Graduate Hospital, 1955–1957

Sign	Number with Symptom	Per Cent
Fever	71	78.9
Râles	57	63.3
Tachycardia	53	58.9
Tachypnea	40	44.4
Hemoptysis	26	28.9
Hypotension	23	25.6
Congestive failure	23	25.6
Friction rub	22	24.4
Rib tenderness	16	17.8
Cyanosis	7	7.8
Jaundice	2	2.2

a normal heart rate was frequently noted when pulmonary embolism developed in fully digitalized patients.

Cyanosis was observed in only 7.7% of our patients, usually during the acute stage of massive pulmonary embolism.

Exquisite local chest tenderness proved to be a valuable diagnostic aid. This sign [29] may be elicited in pneumonia patients who have unusually severe pleuritic pain, but it occurs far more frequently with pulmonary embolism. It is apparently produced by severe spasm of the intercostal muscles secondary to the inflammation of the pleura. When due to pulmonary emboli, it has in our experience resulted from emboli with little or no roentgenologic evidence of infarction. When due to pneumonia, the consolidation is usually quite extensive and readily detected by clinical or radiologic examination.

Clinical jaundice attributed to the effects of pulmonary embolism was encountered only twice in our series. (Jaundice also occurred in five patients with primary hepatic and biliary tract disease.) A third case had subclinical jaundice with slightly elevated serum bilirubin. All of these patients had repeated large pulmonary emboli and right heart failure. The explanation for this relatively low incidence of jaundice as compared to some other series [4, 28] may be the many instances of minor embolism and the relatively few instances of severe congestive failure among our patients. It has been suggested that the hyperbilirubinemia associated with pulmonary embolism is due to lysis of the infarct, i.e., hemolysis, but in all three patients with hyperbilirubinemia the direct-reacting fraction of bilirubin was significantly elevated. Bromsulfalein retention and alkaline phosphatase activity were significantly elevated in one patient; hence hepatic dysfunction rather than hemolysis appears to be the major factor in the icterus that follows infarction.

Abdominal pains were a prominent symptom in 11 patients (12.2%), and constituted the presenting complaint in six. Laparotomy was averted in all but one instance by detection of pulmonary abnormalities by physical or radiologic examination.

Clinical evidence of phlebitis (table 9) was found in 55 patients (61.1%), involving the lower extremities in 53 and the upper extremities

TABLE 9

Relationship of Venous Thrombosis to Pulmonary Embolism
Graduate Hospital, 1955–1957

	Number of Patients
Phlebitis in lower extremities	58
Phlebitis in upper extremities	2
Phlebitis, probably in pelvis	4
Emboli probably of cardiac origin	12
Inadequate examination prior to sudden death	6
Source of emboli unknown	13
	95

TABLE 10

Principal Electrocardiographic Abnormalities in 75 Patients with Pulmonary Embolism

Graduate Hospital, 1955–1957

Abnormality	Number of Patients	Per Cent
Acute cor pulmonale	5	6.7
Coronary insufficiency pattern	18	24.0
Minor positional changes	12	16.0
T wave inversions in right precordial leads	10	13.3
Other abnormalities	8	10.7
No abnormalities	22	29.3

in two patients. Four additional patients with pulmonary embolism had undergone recent pelvic surgery, and it is probable that the source of their emboli was in the pelvic veins. Repeated careful examinations of the extremities from foot to groin and from wrist to axilla for evidence of tenderness along the course of deep veins are necessary in every patient. Thrombophlebitis is extremely common with modern use or abuse of intravenous therapy and, when mild, is often disregarded. Such forms of phlebitis, whether in the upper or lower extremities, occasionally represent an unsuspected source of emboli.[29, 30] However, in spite of meticulous examination, evidence of peripheral thrombophlebitis may not be demonstrable. In 12 of the 55 patients with thrombophlebitis signs of the latter were not present at the time of the embolism but appeared later, sometimes after a week.

The frequency of delayed phlebitis or absence of signs of phlebitis is best explained by the theory [17] that a thrombus is most likely to break loose and form an embolus when it is of recent origin and has not yet resulted in the establishment of an inflammatory process in the surrounding wall of the vein. Only the inflammatory process (phlebitis) is detectable clinically. If the entire thrombus becomes detached and none remains behind to cause an irritative inflammation, no signs of phlebitis may ever result. If part of the thrombus remains, or if another thrombus forms in the same or another vein, the findings of phlebitis may belatedly appear. The important practical implication is that it does not suffice to examine the extremities once, at the time of the suspected embolic episode, but that daily examination for at least a week is mandatory. Furthermore, the absence of signs of thrombophlebitis, while casting some doubt on the diagnosis of thromboembolic disease, by no means rules it out. It should be recognized also that the prompt diagnosis of pulmonary embolism and early institution of anticoagulant therapy will diminish the frequency of appearance of late phlebitis.

Unexplained apprehension has been said to be a frequent premonitory sign of pulmonary embolism.[32] We have encountered apprehension not infrequently following an embolism, as one would in any patient in respiratory distress or with chest pains. In only one patient of the series,

however, did unexplained apprehension appear to precede pulmonary embolism.

The charts of the seven patients in whom the diagnosis of pulmonary embolism was not made until autopsy were reviewed. No symptoms or signs of thrombo-embolic disease were recorded in four patients. In three cases suggestive evidence was described but not recognized as indicative of thrombo-embolism.

Radiologic Findings: Chest roentgenograms were obtained within the week following the embolic episode in 67 patients. In 55.2% of the cases the radiologic reader suggested pulmonary embolism among other possibilities on the basis of the x-ray findings and the clinical history provided on the routine x-ray request form. In an additional 28.4% of cases, significant radiologic findings were present but pulmonary embolism was not among the diagnoses suggested by the radiologist. It should not be inferred that pulmonary embolism and infarction result in pathognomonic x-ray densities. While certain configurations are suggestive of pulmonary embolism and infarction, these diagnoses cannot be made from roentgenographic appearances alone. Furthermore, it is important to realize that the chest roentgenogram may be entirely normal following pulmonary embolism. This is true of major emboli which do not produce infarctions, and of minor emboli which may or may not produce small infarctions at the lung periphery. Some patients may have showers of emboli for years and eventually develop

TABLE 11

Significant Electrocardiographic Abnormalities in 75 Patients with Pulmonary Embolism

Type of Abnormality	Number of Patients	Per Cent
A. Positional changes		
1. Acute cor pulmonale	5	6.7
2. Chronic cor pulmonale	2	2.7
3. Minor positional changes		
Right axis shift	12	16.0
Clockwise rotation	22	29.3
Appearance of R in AVR	18	24.0
Vertical shift	8	10.7
Appearance of S_1	8	10.7
Appearance of Q in III and/or AVF	5	6.7
B. Nonpositional abnormalities		
1. Coronary insufficiency	18	24.0
2. ST-Segment elevations		
In III and AVF	3	4.0
In right precordial leads	6	8.0
3. T-wave inversions in right precordial leads	18	24.0
4. Disturbances of rhythm and conduction		
Transient atrial fibrillation	8	10.7
Transient atrial tachycardia	1	1.3
Sinus tachycardia (in association with other findings)	25	33.3
Transient premature contractions	10	13.3
Right bundle branch block	7	9.3

TABLE 12

Association of Some Nonspecific Electrocardiographic Abnormalities with Positional Changes in Patients with Pulmonary Embolism

Graduate Hospital, 1955–57

Type of Abnormality	Number of Patients	Number with Positional Changes	Per Cent
Coronary insufficiency	18	12	67
T-wave inversions in right precordial leads	18	9	50
Sinus tachycardia	43	25	58
Atrial fibrillation	8	4	50

cor pulmonale [27] without x-ray shadows indicative of infarction. Hampton and Castleman [2] in their fundamental study described a syndrome of incomplete infarction in which hazy densities are visible radiologically for only 24 to 48 hours after embolism. On the other hand, infarction may not be visible during the first 48 hours after embolism and may be missed unless a chest roentgenogram is obtained later.

A detailed analysis of the roentgenologic findings following embolism is in preparation. It is noteworthy that in 13 instances, clinical diagnoses of embolism were not supported by the radiologist, in six cases because the roentgenogram was normal. In seven instances, abnormal densities were present which were regarded by the radiologist as indicative of some other disease. When these films were reviewed for the purposes of the present study, however, it was evident that the changes were entirely consistent with embolism.

It is also of interest that the radiologist called attention to the possibility of pulmonary embolism in 10 patients in whom this possibility had not been suspected clinically.

Electrocardiographic Findings: Seventy-five of the 90 patients in our series had at least two electrocardiograms taken, one shortly after the embolism, another taken either before the embolic episode or several days later serving as control. Significant changes were encountered in 70.7% of these patients (table 10). "*Significant* changes" does not mean pathognomonic changes, which are rarely if ever produced by pulmonary embolism, but rather transient and characteristic abnormalities, whose demonstration in a patient with an appropriate clinical picture supports the diagnosis of embolism. In table 11 are listed all encountered electrocardiographic abnormalities and their incidence. The infrequency with which the classic pattern of acute cor pulmonale was encountered—less than in any other reported series—may again be due to the fact that our series includes many cases of minor emboli which are unlikely to produce a complete acute cor pulmonale pattern. The latter, when observed in a patient with a normal control tracing, indicates acute right ventricular strain due to sudden im-

TABLE 13

Serum Glutamic Oxalacetic Transaminase Levels in 49 Patients with Pulmonary Embolism

Graduate Hospital, 1955–1957

SGO-T Level	Number of Patients	Per Cent
Consistently normal	32	65.3
Above 40 units	17	34.7

pairment of the outflow of blood from the right ventricle. This is almost invariably due to pulmonary embolism, although other pulmonary diseases may occasionally produce acute cor pulmonale.[33] The most important electrocardiographic changes produced by pulmonary embolism and reflected in the acute cor pulmonale pattern are the effects on the electrocardiographic position of the heart. Since positional changes are not ordinarily produced by myocardial infarction, there should be no confusion between acute cor pulmonale and inferior wall myocardial infarction. On the other hand, the appearance of Q waves in Lead AVF is not a reliable sign of myocardial infarction, since it has been reported by others [34] and observed again by us to occur also as part of the acute cor pulmonale pattern as the result of pulmonary embolism.

The pattern of chronic cor pulmonale was encountered in only two of our patients. However, serial tracings in both of these patients revealed transient positional changes, possibly due to recurrent emboli.

While the full picture of acute cor pulmonale was infrequently encountered, "partial" acute cor pulmonale patterns were commonly observed. These consisted of one or more of the components of the full acute cor pulmonale pattern. Smaller emboli obviously have a lesser impact on circulatory dynamics and result in lesser degrees of positional changes of the heart, reflected by one or more of the following: shift of electrical axis to the right; clockwise rotation, manifested by the appearance of S waves over the left precordial leads and R waves in Lead AVR; vertical shifts in the electrical position; the appearance of S waves in Lead I and of Q waves in Leads III and AVF. The occurrence of any of these changes alone was considered to be of some significance, but in most instances two or more of the above changes occurred together (table 12). Three patients with pulmonary embolism manifested no electrocardiographic changes other than the appearance of R waves in AVR, and one patient manifested only transient T wave inversion in Leads III and AVF. Of all the purely positional changes, clockwise rotation (29.3%), with or without R in AVR (24.0%), was encountered most frequently.

As emphasized especially by Dack and associates,[35] the electrocardiographic findings of "coronary insufficiency," manifested by ST segment depressions and T wave inversions over left ventricular leads, may appear following pulmonary embolism. This is seen especially in patients with

TABLE 14

Occurrence of Other Diseases in 17 Patients with Pulmonary Embolism and Elevated Serum Glutamic Oxalacetic Transaminase

Graduate Hospital, 1955–1957

	Number of Patients
Hepatic or biliary disease	7
Myocardial infarction	6
Musculoskeletal injuries	3
No other disease	1

underlying coronary artery disease. Twenty-four per cent of our patients manifested this pattern. What has not, however, been heretofore emphasized is the frequent association of positional changes with those of coronary insufficiency in patients with pulmonary embolism. Of 18 patients with the coronary insufficiency pattern, 12 had such positional changes. The combination is far more suggestive of pulmonary embolism than is the mere appearance of ST-T changes, differing in no way from the findings in coronary insufficiency of other causes.

Intermittent right bundle branch block, incomplete in all but one instance, was seen in seven (9.3%) of our patients. The appearance of P pulmonale waves was noted in one patient.

A more important, yet frequently misinterpreted electrocardiographic finding in pulmonary embolism is the transient inversion of T waves over the right precordial leads. This was noted in 18 (24%) of our patients. These findings may be mistakenly considered as diagnostic of anteroseptal infarction. However, the fleeting nature of these changes, the lack of true coving in many instances and the frequent association with positional changes distinguish the T wave inversions of pulmonary embolism from those of myocardial infarction, in most instances. When the differentiation cannot be made on the basis of electrocardiographic findings alone, the clinical findings and the serum GO-T level (vide infra) will usually help to make the correct diagnosis. The inversion of T waves over the right precordial leads has been studied especially by Sodi-Pallares and associates [34] and has been attributed to right ventricular "strain" and ischemia. Dack and Grishman [36] include these with positional changes as part of the acute cor pulmonale pattern.

Various tachycardias and abnormal rhythms may be precipitated by pulmonary embolism. Because of their nonspecific nature they are of comparatively minor importance in diagnosis, unless they too are associated with suggestive positional changes. The 25 patients listed in table 11 as exhibiting sinus tachycardia did have associated positional changes.

Three patients (4.0%) manifested ST segment elevations in Leads III and AVF, and six patients (8%) manifested some degree of transient ST segment elevation in right precordial "window leads." The latter observation has not, to our knowledge, previously been reported in association with

pulmonary embolism. It was brought to our attention by Dr. David Finkelstein, of the Department of Cardiology of the Graduate Hospital. ST segment elevation in electrocardiographic "window leads," i.e., leads in which an R wave is absent, usually as the result of previous myocardial infarction, and which therefore transmit intracavitary potentials, has been described in association with angina, coronary insufficiency and a positive exercise test.[37, 38] Pulmonary embolism produces these changes, probably through the same mechanism, i.e., by producing coronary insufficiency and subendocardial ischemia registered in cavity or "window leads" as ST-segment elevations.

Serum Glutamic Oxalacetic Transaminase (SGO-T) in Pulmonary Embolism

We have previously reported studies of 26 patients in whom serum glutamic oxalacetic transaminase (SGO-T) levels were determined following pulmonary embolism, and had concluded that significant elevations did not occur after uncomplicated pulmonary embolism.[39] Of the 90 patients in this series, 49 (54.4%) had a total of 126 SGO-T determinations within one to nine days of the date of the diagnosed pulmonary embolism. Of these 49 patients, 32 (65.3%) had consistently normal SGO-T levels, and 17 (34.7%) had one or more elevated SGO-T levels (above 40 units/ml.) (table 13). An analysis of these 17 cases seemed important in an effort to find the cause of the SGO-T elevations. Table 14 lists associated diseases which may have been responsible for the SGO-T elevations. It is evident that in all but one case an adequate explanation for the SGO-T elevation was present. Thus, our preliminary conclusion—that uncomplicated pulmonary embolism is not associated with significant elevations of SGO-T—appears substantiated by additional experience. This is in agreement with the experimental findings of Agress and his associates,[40] and the clinical findings of LaDue and his associates.[41] Ostrow and his co-workers [28] listed pulmonary embolism among the conditions frequently associated with elevations of the SGO-T. This is apparently the result of their failure to distinguish uncomplicated pulmonary emboli from those associated with jaundice.

In our experience, the determination of the level of SGO-T has frequently been helpful in the differential diagnosis of myocardial infarction and cases of pulmonary embolism which simulate myocardial infarction. The determination of SGO-T levels in such cases is of value, moreover, because a normal value 24 to 48 hours after the onset of pain excludes myocardial infarction more speedily than this can be accomplished with other tests.

In cases of unequivocal pulmonary embolism associated with shock, an elevation of the SGO-T level is suggestive of complicating subendocardial myocardial infarction. Three patients showed this sequence. In one who required nor-epinephrine infusions for five days to maintain blood pressure,

the electrocardiogram showed only transient ST segment depression, yet a peak SGO-T level of 406 units was obtained.

It may be superfluous to state that an elevated level of SGO-T should not be regarded as evidence against pulmonary embolism, for embolism may be present in association with myocardial, hepatic or muscular lesions which are responsible for the transaminase elevation.

Discussion

It is believed that the experience which we have reported is typical of that encountered in general hospitals. The occurrence of pulmonary embolism in 1.2% of medical admissions and 0.6% of surgical admissions corresponds quite well to observations made in some other clinical studies, and does not appear excessive when it is considered that the frequency of pulmonary embolism ranges from 10 to 25% in necropsy studies.

Our intensive effort to see all hospital patients with this diagnosis has had the effect of excluding distorted impressions due to overemphasis on cardiac disease or pulmonary disorders. It seems reasonable to consider that approximately 45% of pulmonary emboli present as pulmonary problems, and approximately 35% as cardiovascular problems; in other cases, symptoms may suggest abdominal or neurologic disorders.

We have emphasized the observation that pulmonary embolism is now the most common disease of the lungs encountered in general hospitals; appreciation of this fact should ensure serious consideration of this diagnosis in every acute cardiorespiratory illness. The possibility of pulmonary embolism must be excluded in all patients thought to have pneumonia, pleurisy, myocardial infarction, angina, syncope, and other neurologic and abdominal crises. Physicians must become familiar with the varied clinical manifestations of nonfatal pulmonary embolism if subsequent, perhaps fatal, embolism is to be averted. The diagnosis can be made with considerable accuracy if attention is given to the history and physical examination, including careful study of the extremities, and if there is informed interpretation of the electrocardiogram and chest x-ray films. Determination of serum (SGO-T) transaminase levels is helpful in the differentiation of pulmonary embolism and myocardial infarction.

It is evident from other studies [46] that nonfatal pulmonary embolism is often unrecognized. While the incidence of fatal embolism following surgery is quite similar from one hospital to another, there is variation among hospitals in the frequency with which sublethal embolism is diagnosed. In some hospitals the diagnosis of nonfatal embolism is made less often than is the diagnosis of fatal embolism; in other hospitals, where there is special interest in the detection of this disease, the frequency of nonfatal embolism is reported to be three to nine times that of fatal embolism. If in any hospital the nonfatal instances do not considerably outnumber the fatal cases it must be assumed that the hospital staff is not adequately informed concern-

ing the diagnosis of this disease. It is noteworthy that the hospitals with the highest ratio of nonfatal to fatal embolism—9 : 1—are those whose postoperative mortality from pulmonary embolism is lowest. This experience indicates the practical value of early diagnosis and treatment: we believe it is no coincidence that hospitals which treat many instances of nonfatal embolism encounter fewer instances of fatal embolism.

Effective therapy for this disease is available. Antiembolic therapy may be medical (heparin intravenously or subcutaneously, Dicumarol, or other coumarins or phenindiones) or surgical (vena cava ligation, bilateral femoral vein ligation). Each method has advantages and disadvantages, which will not be enumerated here, but use of any of these methods is greatly to be preferred to inaction. Observations at the Mayo Clinic [7] before the discovery of anticoagulants indicated that if a patient had a postoperative embolism and survived there was a 30.5% chance of another embolism, and an 18.3% chance of fatal embolism in the same convalescence. The 29 postoperative patients in the present study who had nonfatal embolism and were given anticoagulant therapy had no further emboli and, without exception, survived.

Unfortunately, the problem of pulmonary embolism will not be solved entirely by improved diagnosis. Most instances of massive pulmonary embolism give forewarning by minor emboli or by signs of phlebitis that can be detected by the alert clinician. Occasionally, however, fatal embolism occurs without warning and, rarely, fatal embolism occurs in a patient who is receiving what appears to be adequate therapy. Nor have prophylactic efforts been wholly successful. Neither bilateral femoral vein interruption nor administration of anticoagulants routinely to postoperative patients has proved consistently effective. Early ambulation has had many benefits, but it has not materially reduced the frequency of thrombo-embolism.[42] This may be due in some instances to the fact that early ambulation has meant merely early sitting, a posture calculated to increase rather than diminish stasis in the leg veins. Wilkins and Stanton [43] applied elastic stockings to all hospital patients in an effort to increase the linear velocity of blood flow in the deep veins by decreasing their caliber. A significant reduction in the occurrence of pulmonary embolism was achieved by this method, and it would appear worthy of wide use in hospital patients. Attention is called again, however, to the large number of patients with thrombo-embolism in whom this method is not applicable, namely, the patients who develop venous thrombosis prior to hospitalization, often as the result of trivial trauma.[44, 45] More than a third of our patients had thrombo-embolism before hospital admission.

The need for improved methods of diagnosis, prevention and treatment of pulmonary embolism is evident. An essential first step is the recognition of the prevalence of this disorder, and utilization of presently available technics for diagnosis.

Summary

1. Pulmonary embolism has become the most common disease of the lungs encountered in general hospitals. Ninety instances were recognized in an 18-month period at the Graduate Hospital, outnumbering pneumonia and bronchogenic carcinoma.

2. Embolism was preceded by surgery in 33 patients, and by musculoskeletal trauma in six instances. Embolism occurred in 18 patients hospitalized with medical illnesses. In 33 instances, embolism occurred prior to admission to the hospital.

3. Respiratory symptoms predominated in 39 instances, cardiovascular in 33 instances. Abdominal symptoms were most prominent in six patients, and central nervous system manifestations in four. The disease most often requiring differentiation from embolism was acute myocardial infarction.

4. Chest roentgenograms were important in the diagnosis of pulmonary embolism. There was no pathognomonic configuration, but as the Radiologic Department became more alert to the characteristic features of infarction, this possibility was suspected in 55.2% of patients with pulmonary embolism who were x-rayed.

5. Electrocardiographic abnormalities were detected in 70% of cases adequately examined. Typical cor pulmonale patterns were observed in seven patients, transient positional changes in 28, and coronary insufficiency patterns in 18. The high frequency of transient electrocardiographic changes observed is remarkable, since the episodes of embolism were so often of moderate or slight severity.

6. Serum glutamic oxalacetic transaminase determinations were made in 49 patients. Levels were consistently normal in 32 patients, while elevations were noted in 17 patients. In all but one of these, associated hepatic, myocardial or musculoskeletal disease accounted for the elevation. In the absence of these complicating factors, transaminase determinations are valuable in differentiation of pulmonary and myocardial infarction.

7. Pulmonary embolism will be more commonly recognized when it is appreciated as being the most common lung disease now encountered in general hospitals, when this diagnosis is given first consideration in a wide variety of syndromes, and when informed use is made of chest roentgenograms, electrocardiograms, and serum transaminase determinations.

Summario in Interlingua

Embolismo pulmonar es un condition commun que frequentemente escappa al recognition, mesmo in centros de instruction medical. Le majoritate del medicos es familiar con le classic aspectos clinic e laboratorial del condition ben que illos se incontra, de facto, infrequentemente. Es signalate le varietate de syndromes clinic que es producite per embolismo pulmonar. Illo pote manifestar se como problema thoracic, con pleuritis e effusion, hemorrhagia, abscesso, o empyema, o illo pote esser misprendite pro pneumonia postoperatori, neoplasma pulmonar, o tuberculose.

Embolismo pulmonar pote presentar se como problema cardiac, con manifestationes simile a illos de infarcimento myocardial o de angina. Illo pote sequer infarcimento myocardial e simular continuate activitate coronari. Illo pote precipitar disfallimento congestive o esser causate per illo, o il pote occurrer que illo es primo recognoscite quando chronic corde pulmonal se ha disveloppate. Embolismo pulmonar pote presentar se como problema gastroenterologic, con symptomas que simula acute abdomine chirurgic o hepatitis. Embolismo pulmonar pote apparer como un morbo neurologic, con symptomas que suggere un accidente cerebrovascular.

Le presente studio monstra que embolismo pulmonar ha devenite le plus commun morbo del pulmones incontrate in hospitales general. Novanta casos esseva recognoscite al "Graduate Hospital" intra un periodo de 18 menses, i.e. un numero excedente le numero de casos de pneumonia e de carcinoma bronchogene. Embolismo esseva precedite per chirurgia in 33 patientes e per trauma musculoskeletic in sex. Embolismo occurreva in 18 patientes hospitalisate con morbos medical. In 33 casos, embolismo occurreva ante le admission al hospital. Symptomas respiratori predominava in 39 casos, symptomas cardiovascular in 33. Symptomas abdominal esseva le plus prominente in sex patientes, manifestationes de systema nervose central in quatro. Le morbo que le plus frequentemente requireva differentiation ab embolismo esseva acute infarcimento myocardial.

Roentgenogrammas thoracic esseva importante in le diagnose de embolismo pulmonar. Le configurationes roentgenographic non esseva pathognomonic, sed in tanto que le Departimento Radiologic deveniva plus conscie del aspectos characteristic de infarcimento, iste possibilitate esseva suspicite in 55,2 pro cento del patientes con embolismo pulmonar ab qui roentgenogrammas habeva essite obtenite. Anormalitates electrocardiographic esseva detegite in 70 pro cento del casos adequatemente examinate. Typic configurationes de corde pulmonal esseva observate in septe patientes, transiente alterationes positional in 28, e configurationes de insufficientia coronari in 18. Le alte incidentia de transiente alterationes electrocardiographic es remarcabile proque le episodios de embolismo esseva multo frequentemente de moderate o leve grados de severitate. Determinationes de transaminase glutamic-oxalacetic del sero esseva effectuate in 49 patientes. Le nivellos esseva uniformemente normal in 32 casos, durante que elevationes esseva notate in 17. In omne iste 17 casos, con un exception, le elevation esseva explicabile per associate morbos hepatic, myocardial, o musculoskeletic. In le absentia de iste factores complicatori, determinationes de transaminase es de valor in le differentiation inter infarcimento pulmonar e infarcimento myocardial.

Embolismo pulmonar va esser recognoscite plus communmente si tosto que illo es appreciate como le plus commun morbo pulmonar nunc incontrate in hospitales general, si tosto que iste diagnose es prominentemente prendite in consideration in un extense varietate de syndromes, e si tosto que roentgenogrammas thoracic, electrocardiogrammas, e determinationes de transaminase seral es expertemente utilisate.

BIBLIOGRAPHY

1. Belt, T. H.: Thrombosis and pulmonary embolism, Am. J. Path. **10**: 129, 1934.
2. Hampton, A. O., and Castleman, B.: Correlation of post-mortem chest teleroentgenogram with autopsy findings (with special reference to pulmonary embolism and infarction), Am. J. Roentgenol. **43**: 305-326, 1940.
3. Zimmerman, L. M., Miller, D., and Marshall, A. N.: Pulmonary embolism. Its incidence, significance and relation to antecedent vein diseases, Surg., Gynec. and Obst. **88**: 373, 1949.
4. Short, D. S.: A survey of pulmonary embolism in a general hospital, Brit. M. J. **1**: 790, 1952.

5. Collins, D. C.: Pulmonary embolism, based on a study of 271 instances, Am. J. Surg. **33**: 210, 1936.
6. McCartney, J. S.: Post-operative pulmonary embolism, Surgery **17**: 191, 1945.
7. DeBakey, M. E.: A critical evaluation of the problem of thromboembolism, Surg., Gynec. and Obst. **98**: 1, 1954.
8. Israel, H. L., and Pocock, D.: Pulmonary embolism: a major diagnostic problem, J. Philadelphia Gen. Hosp. **3**: 47, 1952.
9. Roe, B. B., and Goldthwaite, J. C.: Pulmonary embolism: a statistical study of post-mortem material at the Massachusetts General Hospital, New England J. Med. **241**: 679, 1949.
10. Moran, T. J.: Pulmonary embolism in non-surgical patients with prostatic thrombosis, Am. J. Clin. Path. **17**: 205, 1947.
11. Towbin, A.: Pulmonary embolism. Incidence and significance, J. A. M. A. **156**: 209, 1954.
12. Bauer, G.: Nine years' experience with heparin in acute venous thrombosis, Angiology **1**: 161, 1950.
13. Kirby, C. K.: Venous thrombosis and pulmonary embolism, S. Clin. North America **26**: 1389, 1946.
14. Kirby, C. K., and Fitts, W. T., Jr.: Thromboembolic complications in surgical patients, Surgery **27**: 564, 1950.
15. Evans, J. A., and Dee, J. F.: Anticoagulant treatment of postoperative venous thrombosis and pulmonary embolism, New England J. Med. **238**: 1, 1948.
16. Farmer, D. A., and Smithwick, R. H.: Thromboembolic disease: a discussion of the problem in surgical patients with particular reference to the fatal embolus, Angiology **1**: 291, 1950.
17. Allen, E. V., Barker, N. W., and Hines, E. A.: Peripheral vascular diseases, 1946, W. B. Saunders Co., Philadelphia.
18. Wolf, L.: Pulmonary embolism, Circulation **6**: 768, 1952.
19. Lillie, R. H., Buxton, R. W., and Duff, I. F.: Prevention and management of thromboembolism, Arch. Surg. **59**: 609, 1949.
20. Carlotti, J., Hardy, I. B., Jr., Linton, R. R., and White, P. D.: Pulmonary embolism in medical patients, J. A. M. A. **134**: 1447, 1947.
21. Vander Veer, J. B., Kuo, P. T., and Marshall, D. S., 2nd: Experiences with venous thrombosis and pulmonary embolism, with special reference to anticoagulant therapy, Am. J. M. Sc. **219**: 117, 1950.
22. Baker, D. V., Jr., Warren, R., Homans, J., and Littman, D.: Pulmonary embolism: evaluation of a policy for prophylaxis and therapy, New England J. Med. **242**: 293, 1950.
23. Anlyan, W. G., Shingleton, W. W., and DeLaughter, G. D., Jr.: Significance of idiopathic venous thrombosis and hidden cancer, J. A. M. A. **161**: 964, 1956.
24. Perkins, R. B., and Bradshaw, H. H.: Pulmonary infarction mistaken for bronchogenic carcinoma, J. A. M. A. **151**: 545, 1953.
25. Hussey, H., and Katz, S.: Pulmonary embolism, GP **12**: 59, 1955.
26. Harvey, J. C., and Sabiston, D. C.: Empyema as a complication of bland pulmonary infarction: consideration of the problem and report of five cases, Ann. Int. Med. **40**: 285, 1954.
27. Owen, W. R., Thomas, W. A., Castleman, B., and Bland, E. F.: Unrecognized emboli to the lungs with subsequent cor pulmonale, New England J. Med. **249**: 919, 1953.
28. Ostrow, B. H., Steinberg, D., Ticktin, H. E., Polis, G. N., and Evans, J. M.: Serum glutamic-oxalacetic transaminase in coronary artery disease, Circulation **14**: 790, 1956.
29. Robertson, C. K.: Points of local chest tenderness in post-operative pulmonary embolism, Edinburgh M. J. **56**: 160, 1949.

30. Loring, W. E.: Venous thrombosis in the upper extremities as a complication of myocardial failure, Am. J. Med. **12**: 397, 1952.
31. Tomlin, E. E.: Pulmonary infarction complicating thrombophlebitis of the upper extremity, Am. J. Med. **12**: 411, 1952.
32. Krause, S., and Silverblatt, M.: Pulmonary embolism, Arch. Int. Med. **96**: 19, 1955.
33. Phillips, E., and Levine, H. D.: A critical evaluation of extremity and precordial electrocardiography in acute cor pulmonale, Am. Heart J. **39**: 205, 1950.
34. Zuckermann, R., Rodriguez, M. I., Sodi-Pallares, D., and Bisteni, A.: Electropathology of acute cor pulmonale, Am. Heart J. **40**: 805, 1950.
35. Dack, S., Master, A. M., Horn, H., Grishman, A., and Field, L. E.: Acute coronary insufficiency due to pulmonary embolism, Am. J. Med. **7**: 464, 1949.
36. Dack, S., and Grishman, A.: Pulmonary embolism and infarction, *in* Clinical cardiopulmonary physiology, edited by B. L. Gordon, 1957, Grune and Stratton, New York.
37. Burchell, H. B., Pruitt, R. D., and Barnes, A. R.: The stress and the electrocardiograms in the induced hypoxemia test for coronary insufficiency, Am. Heart J. **36**: 373, 1948.
38. Klakeg, C. H., and Parkin, T. W.: Elevation of the RS-T segment in the precordial electrocardiogram and ventricular extrasystoles after exercise. Report of a case, Proc. Staff Meet., Mayo Clin. **29**: 97, 1954.
39. Goldstein, F., Israel, H. L., and Seligson, D.: Use of serum transaminase levels in the differentiation of pulmonary embolism and myocardial infarction, New England J. Med. **254**: 746, 1956.
40. Agress, C. M., Glassner, H. F., and Jacobs, H. I.: Serum transaminase levels in experimental pulmonary infarction, Circul. Res. **4**: 220, 1956.
41. LaDue, J. S., Wróblewski, F., and Nydick, I.: Serum glutamic oxaloacetic transaminase activity as an index of acute myocardial damage, Mod. Concepts Cardiovas. Dis. **25**: 333, 1956.
42. McCann, J. C.: Thromboembolism. A comparison of the effect of early postoperative ambulation and Dicumarol on its incidence, New England J. Med. **242**: 203, 1950.
43. Wilkins, R. W., and Stanton, J. R.: Elastic stockings in the prevention of pulmonary embolism. II. A progress report, New England J. Med. **248**: 1087, 1953.
44. Crane, C.: Deep venous thrombosis as the result of effort, New England J. Med. **246**: 529, 1952.
45. Homans, J.: Thrombosis of deep leg veins due to prolonged sitting, New England J. Med. **250**: 148, 1954.
46. Israel, H. L.: The diagnosis of pulmonary embolism. Advances in medicine and surgery, from the Graduate School of Medicine of the University of Pennsylvania, 1952, W. B. Saunders Company, Philadelphia.

ANOMALOUS PULMONARY VENOUS DRAINAGE OF RIGHT LUNG INTO INFERIOR VENA CAVA WITH MALROTATION OF THE HEART: REPORT OF THREE CASES *

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Anomalous pulmonary venous drainage of the right lung into the inferior vena cava is rare. Prior to the advent of angiocardiography the diagnosis was made only at necropsy or operation.[1] Brody in 1942, in a classic review of the literature of anomalous pulmonary venous drainage into the right side of the heart, found only four necropsy reports of anomalous drainage into the inferior vena cava.[2] The first living patient with this anomaly was diagnosed by angiocardiography in 1943 and, together with another case studied with cardiac catheterization, was reported in 1949.[1] Recent reports indicate that there are now about 20 living patients with anomalous pulmonary venous drainage of the right lung into the inferior vena cava recorded in the literature.[3, 4] Bruwer [4] has also reëmphasized the characteristic appearance of the conventional frontal roentgenogram and tomogram, pointing out that such studies are usually sufficient to establish the diagnosis. Nonetheless, angiocardiography by visualizing the anomaly provides the definitive proof.

Seven cases of anomalous pulmonary venous drainage from the right lung into the inferior vena cava have been studied at this center. Three previously reported [1, 5] and a fourth to be reported [6] are similar in appearance, showing some prominence of the right atrium which extends into the right hemithorax, with a multiple-branching vessel in the right lung increasing in size from above downward in a characteristic fashion to merge finally into a broad, crescentic channel adjacent to the right cardiac border. On angiocardiography, an anomalous right pulmonary arterial tree as well as anomalous right pulmonary veins inserting into the inferior vena cava were demonstrated.[1, 5] In the cases herein reported, angiocardiography in two instances also demonstrated the anomalous right pulmonary arterial system, the anomalous right pulmonary venous insertion into the inferior vena cava, and striking malrotation of the heart into the right hemithorax. A similar

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case was reported by Bruwer;[4] anomalous pulmonary venous connections from the right lung into the inferior vena cava were suspected after tomography. Proof was established by cardiac catheterization and selective angiography; bronchoscopic and bronchographic studies indicated either hypogenesis or agenesis of the right lung.

Case Reports

Case 1. A 23 year old asymptomatic seaman was referred to the U. S. Naval Hospital, St. Albans, N. Y., after a routine roentgenogram. Physical examination was normal except that the heart sounds were best heard to the right of the sternum; there were no murmurs. The electrocardiogram was also normal. The frontal roentgenogram (figure 1A) showed marked displacement of the heart into the right hemithorax. The trachea and mediastinum also deviated toward the right side. The left pulmonary artery and branches appeared unduly prominent, while the right upper

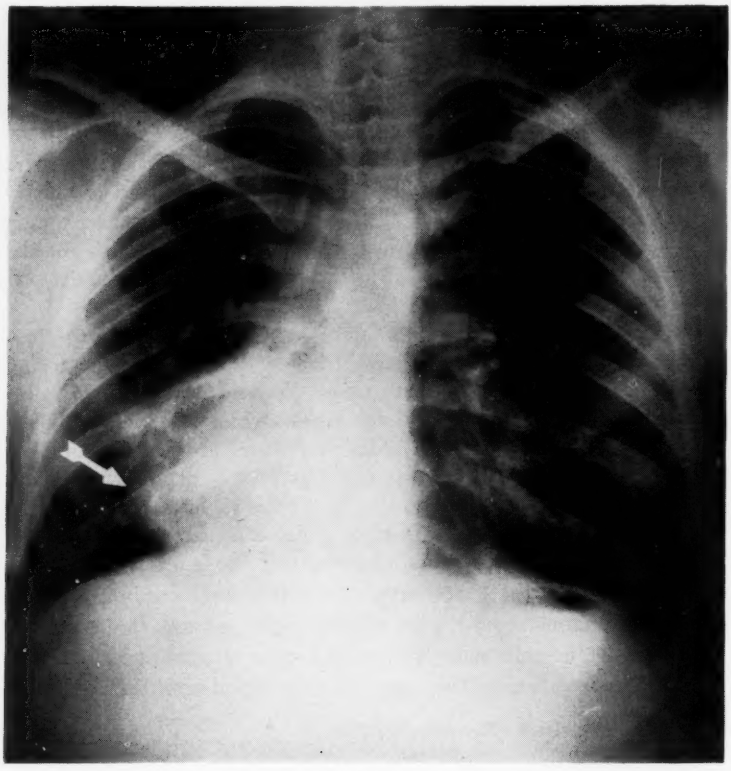

Fig. 1A. *Case 1.* Conventional frontal teleroentgenogram shows rotation of the heart into the right hemithorax. Note the characteristic crescentic branching channel hugging the right cardiac silhouette (arrow). The right upper lung field appears avascular, while the left lung vasculature is unusually prominent.

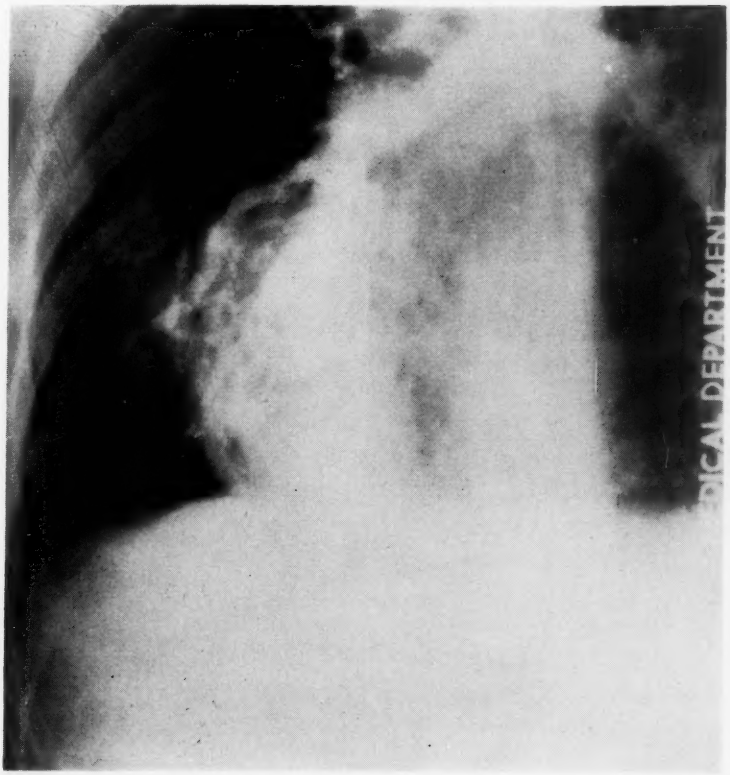

FIG. 1B. *Case 1.* Angiocardiogram 2.5 seconds after beginning of injection discloses rotation of the right cardiac chambers (in the left anterior oblique position, 45°). The pulmonary artery and left branch are also rotated; the right pulmonary artery is hypoplastic. There is diminished vascularity in the right upper lung field; the lower lung field segmental pulmonary arteries are deranged and distorted.

lung vasculature was meager. At the right base, adjacent to the displaced cardiac border, a wide, dense, crescentic shadow merged with the cardiohepatic angle.

Angiocardiography was done on August 18, 1952, with the Fairchild magazine in frontal and lateral views at 0.5 second intervals. It revealed a markedly rotated right atrium and ventricle which on frontal view occupied the position usually seen in the left anterior oblique projection of about 45 degrees. The pulmonary artery, left branch and pulmonary arterial tree were somewhat prominent due to rotation; the right pulmonary artery was diminished in size and its branches were also small, altered in pattern, and few in number at the upper portion of the lung (figure 1B). Opacification of the pulmonary venous system began at 3.5 seconds after the beginning of injection and revealed on the right a large multiple-branching channel of veins inserting into the inferior vena cava (figure 1C). The left pulmonary venous system was normal in size and inserted into the left atrium. The left atrium and ventricle were only slightly rotated and were normal in size. Continued opacification of the

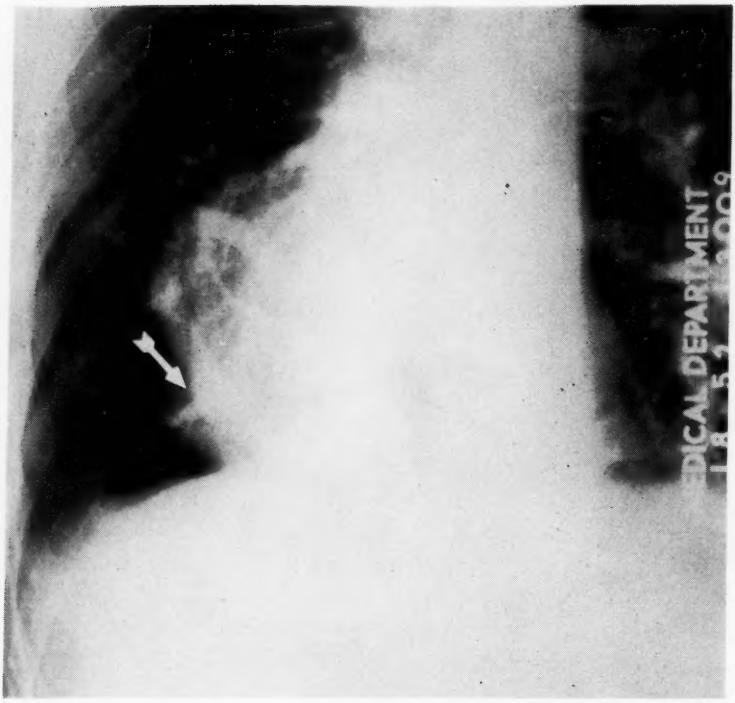

FIG. 1C. *Case 1.* Angiocardiogram 6 seconds after the beginning of injection reveals the right anomalous pulmonary venous channel (arrow) inserting below the diaphragm in the cardiohepatic junction of the heart. The left heart chambers are opacified, and there is also opacification (recirculation) of the left pulmonary artery.

pulmonary artery, especially the left branch and pulmonary arterial tree, occurred during the time of left heart opacification (recirculation).

Case 2. A 23 year old Negro housewife was registered in the prenatal clinic. The patient was asymptomatic, and a routine chest roentgenogram (figure 2A) revealed a heart markedly rotated in the right hemithorax, with displacement of the mediastinal structures. The left pulmonary artery and branches were prominent and in marked contrast to the meager vasculature of the right lung. Although looked for in the conventional frontal roentgenogram, no vascular structures were recognized behind the rotated heart or in the vicinity of the right cardiohepatic area. Physical examination was unremarkable except for evidence of a six months pregnancy. The heart sounds were best heard to the right of the sternum; a systolic murmur (grade 2) was heard to the right of the sternum in the second interspace. The blood pressure was 110/86 mm. of Hg. The electrocardiogram showed normal sinus rhythm, rate 86, and no axis deviation. Multiple right precordial leads were also normal.

Angiocardiography was done on September 18, 1956, following delivery. There was slight enlargement of the right atrium. The atrium, right ventricle and pulmonary artery were markedly rotated in the position usually seen in the left anterior oblique projection of about 45 to 50 degrees. The left pulmonary artery and the pulmonary arterial tree were also rotated and normal in size. The right pulmonary

artery was normal in size at its origin at the bifurcation and then became smaller, with unusual-appearing segmental branches to the mid and lower lung field; the right upper lung field vasculature was markedly diminished (figure 2B). At the time of the pulmonary venous filling (figure 2C) there was a multiple-branching crescentic channel which inserted into the inferior vena cava. The left atrium, ventricle and aorta were normal in size and only slightly rotated. Continued opacification of the left pulmonary artery and pulmonary arterial tree (recirculation) persisted throughout the time of filling of the left heart.

Case 3. A 59 year old woman had had some fatigue and weight loss, and after a routine chest roentgenogram was referred into the hospital on June 20, 1955. The patient had had no previous illnesses, and physical examination was normal save that the position of the maximal impulse of the heart was in the fifth right interspace, 10 cm. from the midsternal line. The blood pressure was 110/80 mm. of Hg. The electrocardiogram showed no deviation of the electrical axis; the heart was in the

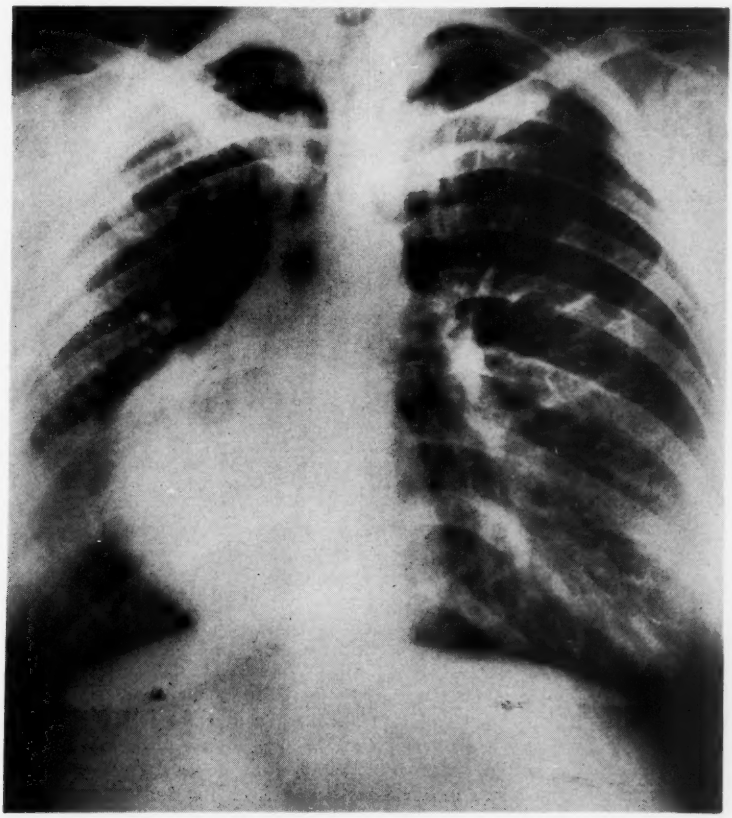

FIG. 2A. *Case 2.* Frontal teleroentgenogram shows rotation of the heart into the right hemithorax. There is avascularity of the right upper lung field; the lower lung field vessels are obscured by the cardiac shadow. Note the prominent left pulmonary artery and pulmonary arterial tree.

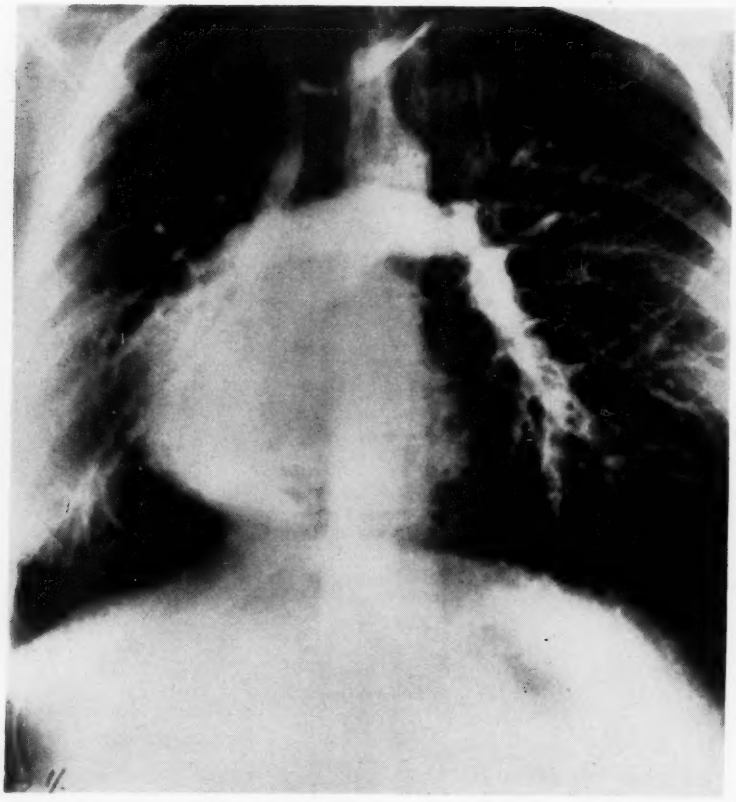

FIG. 2B. *Case 2.* Frontal angiocardiogram at 2.5 seconds reveals the rotated right cardiac chambers, pulmonary artery and branches. On the right the circulation to the upper lobe is meager; the lower lung field segmental vessels appear elongated, with derangement of the vascular pattern.

intermediate position, and the right precordial leads were normal. The chest roentgenograms (figures 3A and B) revealed rotation of the heart into the right hemithorax. There was a large branching vessel which curved downward toward the right cardiohepatic region. A large mass projected into the right posterior hemithorax, best seen in the lateral view (figure 3B), and there was also widespread haziness of the anterior lower two thirds of the right thorax. Barium studies of the gastrointestinal tract failed to show a diaphragmatic hernia.

The vascular pattern of the lower right lung was characteristic of anomalous pulmonary venous drainage into the inferior vena cava. Because of the weight loss and the presence of what appeared to be a pulmonary mass, an exploratory thoracotomy was done by Dr. William A. Barnes on June 29, 1955. This disclosed the right lung to be normal in color but devoid of fissures; the usual trilobar structure was not present. Pulmonary crepitation was normal, and no pulmonary lesions were felt. The lower portion of the lung was densely attached to the diaphragm; in the posterior portion, the diaphragm bulged upward and appeared to be displaced by a firm, retro-

diaphragmatic structure which, although it could not be fully identified, had the consistency of liver. A large vessel, approximately 1.25 cm. in diameter, apparently draining the lung, coursed along the medial portion of the lower part of the lung and entered the diaphragm close to the lateral cardiac border. Examination of the hilum revealed pulmonary arterial blood vessels but no pulmonary veins. The right bronchus was normal in size and location, but the collapsed lung precluded a detailed examination of the branches. The azygos vein and phrenic nerve were in their usual locations. Thick reflections of parietal pleura and pericardium were present anteriorly over the right side of the heart, in the location of the anterior thoracic haziness (figure 3B). There was no chest wall or parenchymal thickening.

The patient made an uneventful recovery and was discharged on July 8, 1955. Recent follow-up examination showed that the patient has continued to be well and asymptomatic.

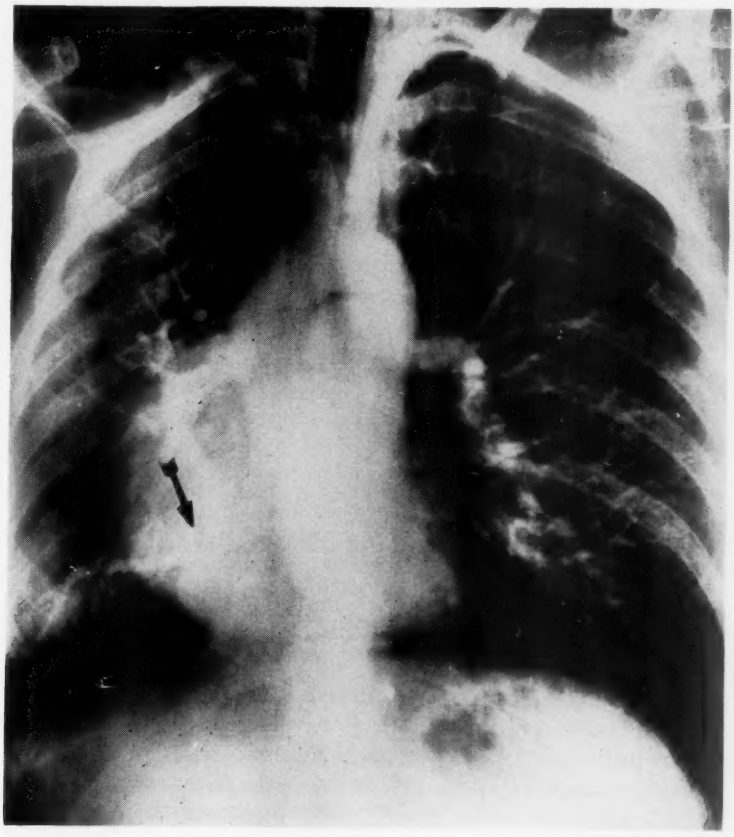

FIG. 2C. *Case 2.* Frontal angiocardiogram at 6.5 seconds discloses the characteristic multiple-branching anomalous pulmonary venous channel (arrow) becoming broad at the right cardiohepatic angle as it enters the inferior vena cava. The left atrium, ventricle and aorta are opacified, and there is re-opacification of the left pulmonary artery, demonstrating the presence of a left-right shunt.

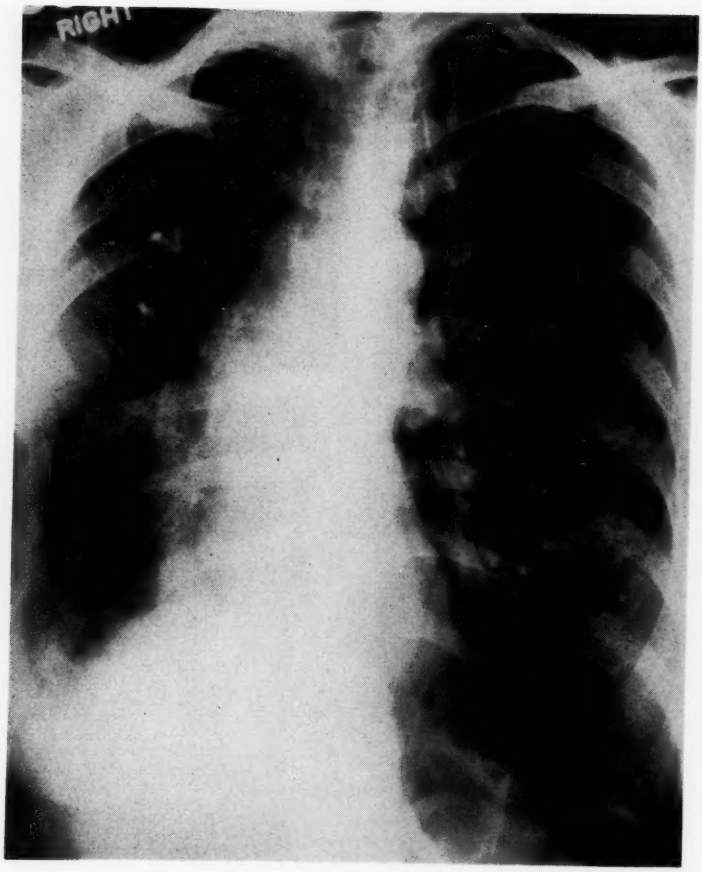

FIG. 3A. *Case 3.* Overpenetrated frontal teleroentgenogram shows a markedly rotated heart into the right hemithorax. There is a large, broad-channeled vessel curving toward the right heart border and right cardiohepatic region. The right lung is hypoplastic, and there is a bulge at the cardiodiaphragmatic area.

DISCUSSION

Anatomic and Physiologic Features: The embryologic features of anomalous pulmonary venous drainage have recently been reviewed [7] and will not be further discussed except to point out that, in the development of the superior vena caval system, persistence of the left cardinal vein (left superior vena cava) [5] and malformations of the pulmonary veins are closely related. Two types of anomalous pulmonary venous drainage are recognized. The *partial* includes insertions of pulmonary veins into the right atrium or its venous tributaries from a lobe or lung. It is occasionally an incidental finding at operation or autopsy and, unless complicated by an associated

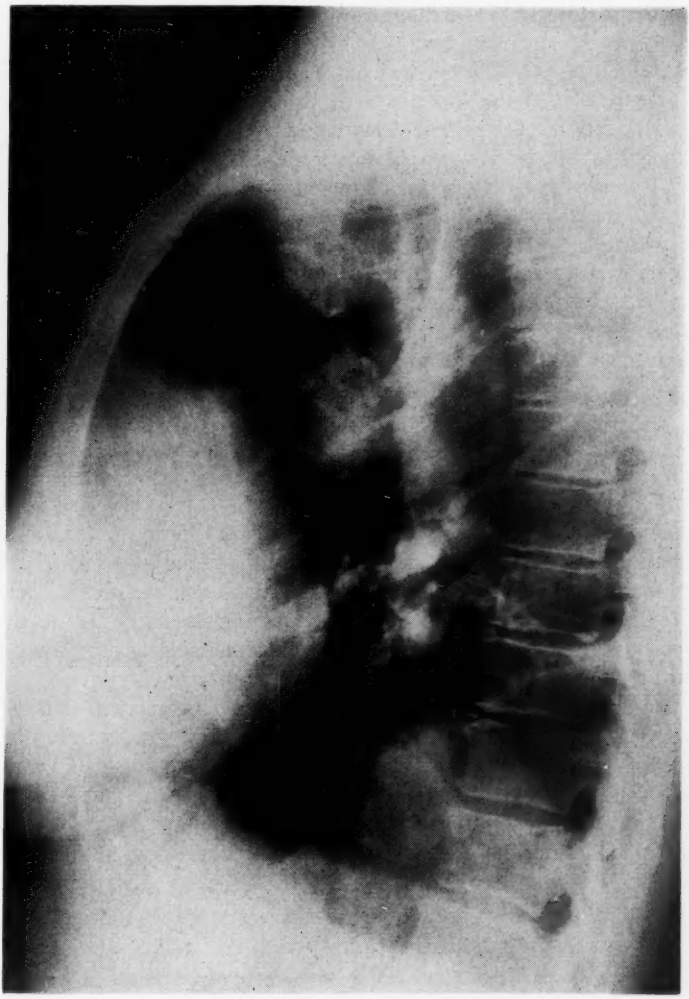

FIG. 3B. *Case 3.* Lateral view reveals massive anterior haziness retrosternally, involving the heart. Note the huge bulge of the posterior part of the right diaphragm.

cardiovascular defect, is compatible with long life. In contrast, *complete transposition of the pulmonary veins* may produce serious symptoms very early in life; long survival has been reported only occasionally.[4, 5] In the total type, an atrial septal defect must also exist to sustain life.

In two cases reported above, proof of the existence of partial anomalous pulmonary venous drainage from the right lung into the inferior vena cava was obtained by angiocardiography, and in the other, surgical exploration

verified the diagnosis. The diagnosis of anomalous insertion of pulmonary veins into the inferior vena cava may also be made by cardiac catheterization studies, which reveal a higher oxygen saturation of the inferior vena caval blood than in that of the superior vena cava and right atrium. An associated atrial septal defect can be determined by advancing the catheter from right to left atrium and by circulation time determinations with methylene blue.[5] The presence of a complicating atrial septal defect in the cases reported above was ruled out by the asymptomatic state of the patients, the normal electrocardiogram, the angiocardiographic findings, and the normal pulmonary vascular pattern of the left lung. (Plethoric lungs are the rule in atrial septal defects.)

None of the seven cases in the series had atrial septal defects. Cardiac catheterization was necessary in only two patients; the first was done in order to establish the identity of the lesion;[1] and the other, to exclude an atrial defect in a dyspneic patient with a diaphragmatic hernia.[6] In the remaining cases, the clinical, electrocardiographic and angiocardiographic evidence was sufficient to exclude the presence of an atrial septal defect. Cardiac catheterization is usually unnecessary in the partial types of anomalous pulmonary venous drainage and should be reserved for symptomatic patients suspected of having complicating lesions such as atrial septal defects.[5]

Anomalies of the right pulmonary arterial system or lung or both have long been recognized in patients with anomalous pulmonary venous drainage into the inferior vena cava. The sparsity of the pulmonary circulation of the right upper lung field and the unusual configuration of the vessels of the lower two thirds of the lung field were noted in the first publication.[1] Recently Bruwer [4] reported bronchoscopic and bronchographic abnormalities of the right lung of a patient with such an anomaly and suggested that hypogenesis or agenesis of a portion of the right lung may be part of the condition. The operative findings of a single, nonlobulated right lung, pleuropericardial adhesions, and partial eventration of the diaphragm in case 3 indicate that multiple thoracic anomalies are often associated with aberrant right pulmonary venous drainage into the inferior vena cava. Slight to moderate increase in size of the right atrium due to the abnormal left-to-right shunting of blood has also long been recognized as a feature of anomalous pulmonary venous drainage of the right lung into the inferior vena cava.[1, 3, 4] Often, the right border of the heart projects well beyond the spine into the right hemithorax. The marked dextrorotation of the heart seen in the three cases described above is apparently not due to dilatation of cardiac chambers. Rather, it appears to be an associated condition. Evidence is lacking and will have to await postmortem study to determine whether the dextrorotation of the heart is an independent embryologic anomaly related to uncomplicated dextroversion,[12] or is a result of the pulmonary parenchymal, pleuropericardial or vascular anomalies.

Clinical Features

Symptoms, Age, Sex and Race: Six of seven patients with anomalous pulmonary venous drainage of the right lung into the inferior vena cava were asymptomatic and were discovered after routine chest roentgenography. For example, one patient, a naval officer, was found to have hypertension on a prepromotion examination, and after the routine chest roentgenogram was suspected of having the anomaly.[1] Another patient had dyspnea and a huge left diaphragmatic hernia. Study of the roentgenogram disclosed the right-sided pulmonary venous anomaly, which was proved by angiocardiography. Cardiac catheterization excluded the presence of an atrial septal defect. The diaphragmatic hernia was thought to cause the dyspnea, and so it proved, for repair of the diaphragm completely relieved the symptom.[6] The ages in seven cases varied from 21 to 59 years. Four were under 40 years and three were over 55 years. Four were male and three female. Only one was a Negro (case 2).

Physical Examination and Electrocardiography: A heart murmur was present in only one patient (case 2), a systolic murmur (grade 2) being heard at the base. In three patients with dextrorotation of the heart (figures 1, 2, 3) the heart sounds were more evident to the right of the sternum. Electrocardiographic studies in all patients were normal and failed to show evidence of increased work of the right ventricle. Two patients with moderate hypertension[1, 5] had slight deviation of the electrical axis to the left. The three patients with rotation of the heart into the right hemithorax, described above, also showed no abnormalities of the right precordial vectors.

Roentgenography: A common feature, observed in six cases of anomalous pulmonary venous drainage of the right lung into the inferior vena cava, was the appearance in the *conventional* frontal roentgenogram of a broad, multiple-branching channel which curved in crescentic fashion near the right cardiac border and descended toward the right cardiohepatic region. In four instances the right atrium was prominent and projected slightly into the right hemithorax. In marked contrast were the cases reported above, wherein there was pronounced rotation of the heart into the right hemithorax. The characteristic vascular deformity adjacent to the right cardiac silhouette could still be detected despite the dextrorotation (figures 1A, 3A). In case 2 (figure 2A) the rotated heart completely obscured the anomalous pulmonary venous vessels, although an overpenetrated film showed the vascular anomaly. Tomography will also reveal the anomalous vascular pattern.[4]

Angiocardiography: Angiocardiography by visualizing the course of the right anomalous pulmonary venous system as it enters the inferior vena cava provides the definitive diagnosis of right pulmonary venous drainage into the inferior vena cava (figures 1C, 2C). In addition, it gives information regarding the cardiac chambers, pulmonary arteries and pulmonary arterial

vasculature (figures 1B, 2B). The size of the chambers, the degree of cardiac rotation, and abnormality of the pulmonary arterial system will also be revealed. Recirculation of blood from the anomalous pulmonary venous system into the right heart structures can also be demonstrated (figures 1C, 2C). Finally, the angiocardiographic findings, coupled with the patient's asymptomatic state and the normal electrocardiographic studies, can be relied upon to exclude a complicating lesion such as an atrial septal defect.

Differential Diagnosis: A pulmonary arteriovenous fistula of the right lower lung field may simulate anomalous right pulmonary veins inserting into the inferior vena cava.[8] However, absence of right atrial prominence and the presence of a vascular bruit should easily differentiate the lesions. An anomalous pulmonary venous trunk may sometimes be obscured by a rotated heart. In such a situation, congenital absence of the right pulmonary artery may come to mind because of the mediastinal and cardiac shifting.[9] Absence of the right pulmonary arterial tree and the "lacy" pattern of the vasculature should suggest the bronchial rather than the pulmonary arterial circulation. Diminished breath sounds due to hypoplasia of the right lung and physical and x-ray signs of overdistention of the opposite lung will also give clues to the diagnosis. Finally, a patient with anomalous systemic arteries from the abdominal aorta perforating the diaphragm and entering a hypoplastic right lung may, because of cardiac dextrorotation and right pulmonary hypoplasia, be difficult to distinguish from anomalous right pulmonary veins draining into the inferior cava cava.[10] Clinically, in such a case, disabling dyspnea may be present.[11] Without angiocardiography it would indeed be difficult to establish the diagnosis.

Experience gained from study of the above three cases indicates the need for reëvaluation and careful examination of the right vascular pattern of patients with dextrorotation of the heart. In addition to the gastrointestinal and electrocardiographic studies of patients suspected of having dextrocardia, overpenetration of the frontal roentgenogram, tomography and angiocardiography are indicated to exclude pulmonary vascular anomalies of the right lung.

Treatment

Asymptomatic patients with partial anomalous drainage of the right lung into the inferior vena cava do not require treatment, this anomaly being compatible with long life. Patients with dyspnea, recurrent pulmonary infections and plethora of the lungs should be suspected of having an associated cardiac lesion, such as an atrial septal defect. In such an event, cardiac catheterization in order to assess the amount of the shunt and the degree of damage to the right ventricle (hypertension) is recommended. Present day corrective heart surgery may be expected to alleviate the atrial septal defect and correct the anomaly.[4]

Summary

Three asymptomatic patients with marked rotation of the heart into the right hemithorax were found to have anomalous pulmonary venous drainage from the right lung into the inferior vena cava. In two, the characteristic appearance of the multiple-branching crescentic trunk adjacent to the right cardiac border in the conventional roentgenogram was a significant clue in diagnosis. In the other, the anomalous channels were obscured by the heart. Angiocardiography provided the definitive diagnosis in two cases and was useful in demonstrating the degree of cardiac and pulmonary arterial rotation. Of great importance was the demonstration of the anomalous right pulmonary arterial tree, the presence of a left-right shunt (recirculation of blood) and absence of an atrial septal defect. Anomalies of the right lung, pleura, diaphragm and bronchial tree may be a factor in cardiovascular rotation. In the absence of further proof, it is probable that the malrotation of the heart is an accompanying condition. Scrutiny of the right lower lung vasculature of patients with dextrocardia and dextroversion of the heart is recommended in order not to overlook vascular anomalies of the right lung.

Addendum

Since this paper was submitted for publication, Halasz et al.[13] reported three cases of anomalous pulmonary venous drainage into the inferior vena cava. There were associated anomalies of the right lung; abnormal arrangements of the bronchi, bronchial diverticula, arterial branches from the aorta and a hypoplastic pulmonary artery.

Acknowledgments

Thanks are due to Dr. B. H. Kean for permission to report case 3, and to Dr. William A. Barnes for the operative findings.

Summario in Interlingua

In casos classic, anormal drainage del venas dextero-pulmonar a in le vena cave inferior es recognoscibile in frontal roentgenogrammas conventional. On vide alora un vaso multi-canalate que se face plus large verso le base del pulmon e se curva lateralmente verso le silhouette dextero-cardiac ubi illo se reuni con le angulo cardiohepatic. Le atrio dextere es prominente e le pulmon hypoplastic. In un serie de 7 patientes, 3 habeva malrotation del corde. In 2, angiocardiographia revelava dexterorotation de structuras cardiovascular, anormal brancas del arterias dextero-pulmonar, e drainage pulmono-venose a in le vena cave inferior. Thoracotomia in 1 caso demonstrava multiple anormalitates: Un sol pulmon sin division in lobos, adhesiones pleuropericardial anterior, e eventration partial del diaphragma.

BIBLIOGRAPHY

1. Dotter, C. T., Hardisty, N. M., and Steinberg, I.: Anomalous right pulmonary vein entering the inferior vena cava: two cases diagnosed during life by angiocardiography and cardiac catheterization, Am. J. M. Sc. **218**: 31–36, 1949.
2. Brody, H.: Drainage of the pulmonary veins into the right side of the heart, Arch. Path. **33**: 221–240, 1942.

3. McKusick, V. A., and Cooley, R. N.: Drainage of right pulmonary vein into inferior vena cava: report of a case with a radiologic analysis of the principal types of anomalous venous return from the lung, New England J. Med. **252**: 291–301, 1955.
4. Bruwer, A. J.: Posteroanterior chest roentgenogram in two types of anomalous pulmonary venous connection, J. Thoracic Surg. **32**: 119–134, 1956; Am. J. Roentgenol. **76**: 664–692, 1956.
5. Sepulveda, G., Lukas, D. S., and Steinberg, I.: Anomalous drainage of pulmonary veins: clinical, physiologic and angiocardiographic features, Am. J. Med. **18**: 833–899, 1955.
6. Steinberg, I., and Lukas, D. S.: Angiocardiography in the diagnosis of anomalous pulmonary venous drainage, to be published.
7. Edwards, J. E., and Helmholz, H. F.: A classification of total anomalous pulmonary venous connection based on developmental considerations, Proc. Staff Meet., Mayo Clin. **31**: 151–160, 1956.
8. Steinberg, I., and McClenahan, J.: Pulmonary arteriovenous fistula: angiocardiographic observations in nine cases, Am. J. Med. **19**: 549–568, 1955.
9. Steinberg, I., Dotter, C. T., and Lukas, D. S.: Congenital absence of a main branch of the pulmonary artery, J. A. M. A. **152**: 1216–1218, 1953.
10. Steinberg, I.: Angiocardiography in pulmonary disease, Am. J. Surg. **89**: 215–230, 1955.
11. Maier, H. C.: Absence or hypoplasia of a pulmonary artery with anomalous systemic arteries to the lung, J. Thoracic Surg. **28**: 145–162, 1954.
12. Welsh, R. H., and Felson, B.: Uncomplicated dextroversion of the heart, Radiology **66**: 24–32, 1952.
13. Halasz, N. A., Halloran, K. H., and Liebow, A. A.: Bronchial and arterial anomalies with drainage of the right lung into the inferior vena cava, Circulation **14**: 826–846, 1956.

OBSERVATIONS IN THE TREATMENT OF HYPERTHYROIDISM WITH I^{131} *

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Introduction

Within the last decade radioactive iodine has become the therapeutic agent of first importance in the treatment of hyperthyroid disease. It is commonly accepted as the treatment of choice in Graves's disease,[1, 2] and has been used in the treatment of other types of hyperthyroidism.

There continues to be disagreement as to the advisability of its use for younger people, in certain types of goiter, and with reference to exophthalmos.[3, 6] Dosage is still somewhat empiric, though related mathematically to the estimated size of the thyroid and the tracer dose uptake.[7, 12] It is our purpose to relate briefly our own five-year experience in the treatment of hyperthyroidism with radioactive iodine and to furnish a statistical analysis of controversial factors.

Material

These observations were made on 106 consecutive cases treated with radioactive iodine at the Protestant Deaconess Hospital, beginning with the first case so treated. The average observation period after treatment is 14 months, the longest 36 months, and the shortest period has been six months after treatment. The patients were unselected except that we have declined to treat pregnant women. The classification as to age is given in table 1. It may be noted that 39% of all cases are less than 40 years old, and 6% are adolescents; 86% of the total number are female, 13% of all cases had previ-

Table 1

Age Distribution

Decades	I	II	III	IV	V	VI	VII	VIII	IX
No. of cases	0	6	13	22	22	18	19	6	0
% of total cases	0	6	12	21	21	16	18	6	0

The cases are unselected as to age; 39% of the treated cases are less than 40 years of age, and 6% are adolescents.

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TABLE 2

A Conventional Classification of Hyperthyroid Disease with the Number of Cases in Each Class

Type of Goiter	No. of Cases	% of Total Cases
Diffuse goiter with exophthalmos	38	36
Diffuse goiter without exophthalmos	44	41
Nodular goiter with exophthalmos	3	3
Nodular goiter without exophthalmos	11	10
Solitary toxic nodule	4	4
No demonstrable thyroid enlargement	6	6

ously had thyroidectomy, and 19% have thyrocardiac disease. Distribution of cases with respect to type of goiter is given in table 2.

METHOD

It has been and is our purpose in the treatment of hyperthyroidism with radioactive iodine to administer one curative dose, the size determined by the estimated weight of the thyroid gland and the greatest iodine uptake measured by tracer study. Originally we resorted to palpation to estimate thyroid size, but in most of these cases the size has been more accurately judged by graphic delineation with a scintiscanner. We have made use of the formula $W = A \times H \times .32$,[13] in which W is the weight of the gland expressed in grams, A is the frontal area as measured in square centi-

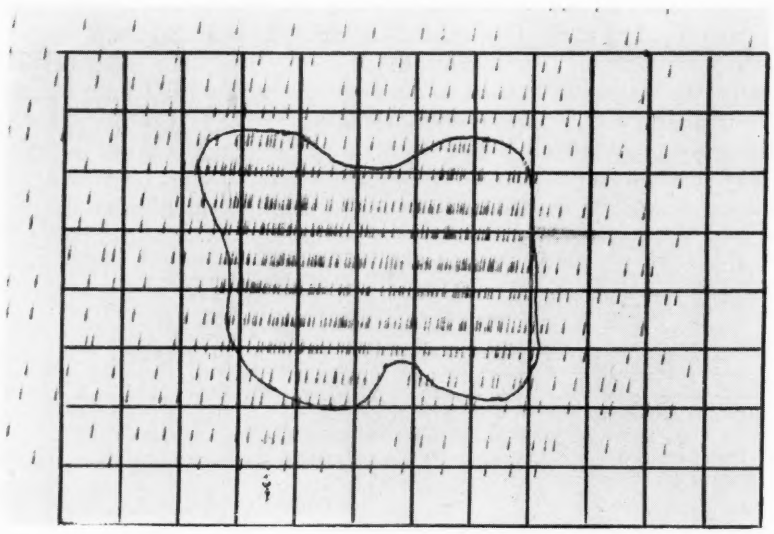

FIG. 1. A thyroid scintigram. The determination of thyroid weight by the formula $W = A \times H \times .32$. In this case the height of the lateral lobes is 4 cm. and the frontal area is 20 cm.^{2} By substitution in the formula we find the gland weighs 24 gm.

TABLE 3

Magnitude of I^{131} Therapeutic Dose

No. of Mc.	No. of Cases	% of Total Cases
Less than 6	19	19
6–10	45	42
11–15	29	27
16–20	9	8
21 or more	4	4

Smallest single dose—2.25 mc.
Largest single dose—25.0 mc.

meters, and H is the average height of the lobes. Figure 1 illustrates the determination of thyroid weight from a scintigram.

The dose, though variable as to the determined weight of the thyroid gland, is expressed as microcuries of I^{131} per gram. The magnitude of the therapeutic dose is given in table 3. The smallest dose given is 2.25 mc., and the greatest single dose is 25 mc. When the initial dose has been inadequate, additional treatment is given after an interval of three months. It will be noted in table 4 that 76% of all cases required only one dose.

RESULTS

Eighty-six per cent of all treated cases become euthyroid, and an additional 7% are permanently hypothyroid after complete treatment. Thus hyperthyroidism is effectively controlled in 93% of the cases so treated. Four of the treatment failures are in nodular goiters, so that in the treatment of Graves's disease only 4% (three cases) remain uncontrolled. Of the cases of nodular goiter, 22% are hyperthyroid after intervals of more than six months after receiving treatment. Both the dose and the period of observation were thought to be adequate.

The dose of I^{131} expressed in microcuries per gram of thyroid tissue is listed in table 5, with related effect. With the dose greater than 80 microcuries per gram there has been no persistence of hyperthyroidism in cases of Graves's disease, and there has been no greater incidence of permanent hypothyroidism above this dose level. We also note that when the dose is greater than 120 microcuries per gram there has been no persistence of

TABLE 4

Number of Doses of I^{131}

	No. of Cases	% of Total Cases
1 Dose	81	76
2 Doses	18	17
3 Doses	3	3
4 Doses	4	4

A single dose was adequate in the great majority of cases. Most of the cases requiring more than one dose were nodular goiters.

TABLE 5

Dose to Thyroid Gland Expressed as Microcuries per Gram	Thyroid Functional Status After I^{131} Therapy	Diffuse Goiters, Number of Cases	Nodular Goiters, Number of Cases	All Goiters, Number of Cases
<40 μc./gm. Smallest dose 33 μc./gm.	1. Hyperthyroid	1. 1	1. 2	1. 3
	2. Euthyroid	2. 3	2. 0	2. 3
	3. Hypothyroid	3. 0	3. 0	3. 0
41–80 μc./gm.	1. Hyperthyroid	1. 2	1. 1	1. 3
	2. Euthyroid	2. 20	2. 2	2. 22
	3. Hypothyroid	3. 2	3. 0	3. 2
81–120 μc./gm.	1. Hyperthyroid	1. 0	1. 1	1. 1
	2. Euthyroid	2. 26	2. 4	2. 30
	3. Hypothyroid	3. 1	3. 0	3. 1
121–160 μc./gm.	1. Hyperthyroid	1. 0	1. 0	1. 0
	2. Euthyroid	2. 11	2. 3	2. 14
	3. Hypothyroid	3. 4	3. 0	3. 4
161–200 μc./gm.	1. Hyperthyroid	1. 0	1. 0	1. 0
	2. Euthyroid	2. 7	2. 3	2. 10
	3. Hypothyroid	3. 0	3. 0	3. 0
>200 μc./gm. Largest dose 375 μc./gm.	1. Hyperthyroid	1. 0	1. 0	1. 0
	2. Euthyroid	2. 11	2. 2	2. 13
	3. Hypothyroid	3. 0	3. 0	3. 0

The thyroid weight is estimated by the method described in the text and the number of microcuries per estimated gram calculated from uptake studies. In Graves's disease there is no persistence of hyperthyroidism in dose range of 81 to 120 mc. per gram, and the incidence of hypothyroidism is no greater above this level than below it. It will be noted that there is no case of induced hypothyroidism in any case of nodular goiter, but the size of the dose for control of hyperthyroidism is larger.

hyperthyroidism, even in nodular goiters, and there is no dose up to and including 375 microcuries per gram that produces permanent hypothyroidism in a nodular goiter.

Exophthalmos was observed in 41 cases of the series, one of which appeared after treatment. Of the remaining 40 cases, two are unchanged by treatment, 17 are improved and 21 are entirely cured. Of the cases with enlargement of the thyroid gland, 79% are reduced to normal size and 14% have diminished size after treatment. Manifest nodules appeared after treatment in 7% in which reduction in thyroid size was effected. Those removed surgically have been proved to be adenomas.

In addition to the cases of permanent hypothyroidism after I^{131} therapy, there were 12 cases of temporary hypothyroidism that became euthyroid within six months. We attribute to treatment one instance of mild exacerbation of hyperthyroidism, two cases of mild transient thyroiditis, and one case of breast hypertrophy in a mature female. The breasts became large, red and painful one month after treatment, and a year later are still large but no longer red or painful. In a review of the literature we have not found another instance of such a complication.

Discussion

While the opinion has often been expressed that only people in an older age group should be treated with radioactive iodine, we find those reporting on the therapeutic use of this drug invariably find occasion to treat adolescents and children, and they frequently constitute a significant percentage of the total group. It has been our observation that the younger individuals required larger dosage, but the ultimate response to treatment was comparable to that attained in the adult group. Any allegation as to carcinogenesis is purely speculative and will remain so for many years to come. Now, within the second decade of the use of I^{131}, there has been no authentic report as to malignant disease incident to its use, and we would be quite reluctant to forego the obvious advantages of this therapeutic agent because of the very remote chance of induced malignancy.[14]

Classification of the type of goiter is important. Results in the treatment of nodular goiter are less favorable than in Graves's disease, and the prognosis as to cure must be guarded. The dosage of radioactive iodine for the desired effect is larger. If large nodules are present they are readily discernible by palpation. We have had some success in demonstrating smaller nodules by the scintigram.

In contrast to the less predictable result obtained in the nodular hyperthyroid disease, the complete remission is almost a certainty in Graves's disease. This degree of control of hyperthyroidism is accomplished with no greater incidence of hypothyroidism than is encountered with surgical management, and none of the other rather common surgical complications. Furthermore, the strikingly good effect on exophthalmos would seem to make it the only logical therapy when this condition is present.

Complications other than permanent hypothyroidism have not been a problem. Transient hypothyroidism is encountered in a significant percentage of cases, but minimal doses of thyroid extract have kept the symptoms under control until the gland resumed normal function. The single case of transient aggravation of the symptoms of hyperthyroidism, the two cases of mild thyroiditis of brief duration, and four cases of nodules appearing after therapy have not appreciably detracted from the excellence of therapeutic results. The nodules which were detectable after treatment were benign adenomas as demonstrated microscopically.

There seems to be no correlation between the size of the dose and the incidence of permanent hypothyroidism. All cases of Graves's disease were controlled with doses of 80 to 120 microcuries per gram of thyroid tissue. The oral dose in the average case requiring treatment will be 7 millicuries. There was no case of induced hypothyroidism following treatment of nodular goiters even when very large doses were used. In those cases of nodular goiter in which for some reason treatment with I^{131} is clinically preferred, the recommended dose range is 120 to 160 microcuries per gram. Treatment with a single dose of I^{131}, rather than multiple smaller doses, is pre-

ferred. This preference is based on mathematical dose determination which is not available to us after an initial dose. Furthermore, the therapeutic response is more prompt and the incidence of complication no greater.

Summary

1. A statistical analysis of 106 cases of hyperthyroid disease treated with I^{131} is presented.

2. The treatment of Graves's disease is highly satisfactory, the treatment of nodular goiter less effective, although still useful when surgery is contraindicated.

3. Regression of exophthalmos is superior to surgical results, and the incidence of complications as compared to surgical treatment is much less.

4. Age is not considered a deterrent factor in the use of I^{131}.

Summario in Interlingua

Iodo radioactive ha non essite acceptate universalmente como agente therapeutic pro omne casos de hyperthyroidismo. Nos ha usate lo in le tractamento de 106 hyperthyroidicos, completemente non seligite—excepte que nos ha refusate tractar gravidas. Le majoritate del patientes assi tractate esseva adulte e feminin, sed 39 pro cento habeva minus que 40 annos de etate, e sex pro cento esseva juveniles.

Esseva nostre objectivo administrar un sol dose curative, basate super le peso del glandula thyroide e su capacitate a acceptar I^{131}. Le peso del glandula thyroide esseva calculate super le base del scintillogramma.

Le resultatos es basate super un periodo medie de 14 menses de observation post le tractamento. Le hyperthyroidismo de 93 pro cento del casos tractate esseva regulate efficacemente, incluse septe casos que deveniva permanentemente hypothyroide. Le 88 casos classificate como diffuse struma toxic includeva solmente tres casos de non-successo therapeutic. In omne istos, minus que 81 mc de I^{131} per g de tessuto thyroide habeva essite administrate. Quatro non-successos occurreva inter le 18 casos de nodular struma toxic. In omne iste quatro casos, minus que 121 mc/g habeva essite administrate. Nulle non-successo therapeutic occurreva in casos in que le dose esseva plus que 120 mc/g. Novanta-tres pro cento del patientes con definite allargamento thyroide experientiava appreciabile reductiones del dimension strumal. Exophthalmo esseva curate o grandemente meliorate in omnes, excepte duo, de 40 patientes. Le complicationes esseva leve e pauco frequente.

In le tractamento de morbo de Graves, I^{131} es apparentemente le agente de election. Iste forma de therapia es libere del risco, del expensas pro hospitalisation, e del incommoditate que characterisa thyroidectomia. Il es ver, strumas nodular require plus grande doses pro comparabile effectos e non responde per le mesme excellente resultatos, sed in iste categoria de casos le methodo a I^{131} es a recommendar pro patientes in qui intervention chirurgic non es indicate.

Nos non cognosce ulle observation capace a corroborar le hypothese de carcinogenese per iodo radioactive, e nos non crede rationabile suspicer un adverse effecto genetic. Nos opina que le obvie beneficios immediate que resulta del uso de I^{131} annulla le improbabile allegation que iste agente produce cancere o mutation.

BIBLIOGRAPHY

1. Hamwin, G. J., and Goldberg, R. F.: The modern treatment of thyrotoxicosis, Arch. Int. Med. **97**: 453–465, 1956.

2. Feitelberg, S., Kaunitz, P. S., Solomon, S. N., Wasserman, L. R., and Yohalem, S. B.: Hyperthyroidism; treatment with radioactive iodine, Arch. Int. Med. **85**: 471–478, 1950.
3. Cook, J. R., Jones, R. W., and McCullagh, E. P.: Treatment of toxic adenomatous goiters by large doses of radioactive iodine, J. Clin. Endocrinol. and Metabolism **15**: 1512–1517, 1955.
4. Beierwaltes, W. H., and Johnson, P. C.: Hyperthyroidism treated with radioiodine, Arch. Int. Med. **97**: 393–402, 1956.
5. Chapman, E. M., and Evans, R.: Treatment of toxic goiters with radioactive iodine, M. Clin. North America **33**: 1211–1223, 1949.
6. Werner, S. C., Quimby, E. H., and Schmidt, C.: Clinical experience in diagnosis and treatment of thyroid disorders with radioactive iodine, Radiology **51**: 564–581, 1948.
7. Clark, D. E., Rule, J. H., Tripple, O. H., and Cofrin, D. A.: Five year experience with radioactive iodine in treatment of hyperthyroidism, J. A. M. A. **150**: 1269–1272, 1952.
8. Seed, L., and Jaffe, B.: Comparison of tracer dose and therapeutic dose of I^{131} as to thyroid uptake, effective half life and roentgen dosage, Radiology **63**: 551–561, 1954.
9. Stone, H., Catz, B., Petit, D., and Starr, P.: Therapeutic studies in hyperthyroidism; use of radioactive iodine, California Med. **81**: 4–6, 1954.
10. Balls, K. F., Chamberlain, R. H., Rose, E., Gorson, R. O., and Blount, H. C., Jr.: The treatment of thyrotoxicosis with radioiodine, Radiology **64**: 858–866, 1955.
11. Haines, S. F., Keating, F. R., Jr., Power, M. H., Williams, M. M. D., and Kelsey, M. P.: Use of radioiodine in treatment of exophthalmic goiter, J. Clin. Endocrinol. and Metabolism **8**: 813–825, 1948.
12. Williams, H., Towery, B. T., Jaffe, H., Rogers, W. F., Jr., and Tagnon, R.: Radiotherapeusis, Am. J. Med. **7**: 702–717, 1949.
13. Kelly, F. J.: Observations on the calculation of thyroid weight using empirical formulae, J. Clin. Endocrinol. and Metabolism **14**: 326–335, 1954.
14. Quimby, E. H., and Werner, S. C.: Late radiation effects in roentgen therapy for hyperthyroidism; their possible bearing on the use of radioactive iodine, J. A. M. A. **23**: 1046–1947, 1949 (Letter to the Editor).

DISABILITY TWO TO FIVE YEARS AFTER MITRAL COMMISSUROTOMY: AN EVALUATION BY CLINICAL CRITERIA AND EXERCISE TOLERANCE *

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Mitral commissurotomy has been advocated by many for relief of disabling mitral stenosis in properly selected patients. Since this lesion is only one of the pathologic features responsible for the cardiac disability, it is important to evaluate as objectively as possible the benefits derived from surgery.

In the broadest interpretation there are two important results to evaluate: prolongation of longevity, and reduction in degree and duration of disability. Prolongation of life cannot be clearly evaluated until all patients have been followed up to the time of death. Comparative analysis of the symptoms of disability is limited by the highly subjective nature of criteria usually employed, as well as by numerous variables in the course of disease and treatment over the entire period of observation. Furthermore, interpretation of observations in surgically treated patients is difficult, due to limited information regarding the course of disability in patients with mitral stenosis treated concomitantly by medical measures only.

The purpose of this report is to describe disability and mortality in patients who were followed from two to five years after mitral commissurotomy. Results are further evaluated by comparison with available unoperated patients and published reports of follow-up studies on unoperated patients. In addition, clinical factors of prognostic value in the selection of patients for this operation have been assessed.

Material

Patients selected for study were those previously referred to the laboratory who satisfied the following criteria:

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From the University of Washington School of Medicine, Seattle, Washington.

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† Trainee of the National Heart Institute, 1954–1955.

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1. Predominant mitral stenosis.
2. Symptoms and disability due to pulmonary congestion and/or repeated peripheral emboli.
3. Observation, including serial tests of exercise tolerance, for two or more years previously.

Of 58 survivors of mitral commissurotomy who had satisfied these criteria, 48 (83%) returned for examination. (Of the 10 survivors not seen, four had moved to distant areas, two were in good health but unable to return, and the remaining four were lost to follow-up.) Fourteen unoperated survivors likewise returned, about 70% of those with whom we were in contact. In addition to these survivors, the records of patients who died at operation or during the follow-up period were also studied (table 1). Two patients in the unoperated group died within 13 months of initial evaluation and were considered early deaths. Nine patients in the operated group died during hospitalization for operation and were likewise considered early deaths. Three operated patients died of their heart disease from two to four years following operation and were considered late deaths.* Altogether, 60 operated and 16 unoperated patients were studied.

TABLE 1

Analysis of Case Material According to Management and Course*

	Unoperated Patients			Operated Patients		
	Contra-indicated	Refused	Total	"UW"	"Other"	Total
Initial number	13	3	16	46	14	60
Early deaths	2	0	2	5	4	9
Survived 2 years	11	3	14	41	10	51
Late deaths	0	0	0	2	1	3
Remaining survivors	11	3	14	39	9	48

* Omitting six unoperated and 10 operated patients on whom it was impossible to obtain a final follow-up evaluation by personal examination.

Forty-six of the patients, who were operated upon by one of us (K. A. M.), are referred to as the "UW" group. Fourteen additional patients, who were operated upon by other surgeons, were included to increase the number of cases studied. These are referred to as the "other" group. Indications for operation were: disability 55 patients; disability first appearing in pregnancy, three; arterial emboli, two.

Contraindications to operation in 13 unoperated patients were: insufficient disability, eight; probability of active carditis, with or without insuf-

* B. W., previously reported elsewhere,[1] was omitted because of failure to satisfy the third criterion. He had predominant mitral regurgitation at operation, pancarditis on auricular biopsy and progressive deterioration from heart failure; he died one year after operation, with autopsy evidence of myocarditis.

ficient disability, three; severe disability with inadequate reserve, two. There were three other patients without contraindications who refused operation.

Follow-up period averaged 3.9 years (range from two to five years) in unoperated patients, and 3.7 years (range from two to five years) in operated patients.

Methods

Initial * and final evaluation consisted of history and physical examination, chest fluoroscopy and 12-lead electrocardiogram. Pertinent clinical findings were graded on a scale of 0 to 3 plus (corresponding to none, slight or doubtful, moderate and marked degree, respectively) for purposes of quantitation. The intensity of murmurs was graded from 1 to 6, as described by Levine and Harvey.[2] Exercise tolerance was evaluated by a standardized test employing grade walking on a motor-driven treadmill. Results were expressed as a physical fitness index, with normal range considered to be from 13 to 26.[3] Right heart catheterization was done during initial evaluation of many patients.

Improvement on comparison of final with initial * clinical evaluation was ascertained by the following criteria:

1. Patient's opinion.
2. Functional capacity (New York Heart Association).
3. Physician's opinion, based upon changes in ordinary daily activity that may have affected the evaluation of symptoms and limitations.
4. Physical fitness index of exercise tolerance.

A combination of all four criteria was also used to adjust for individual discrepancies.

Operated survivors were divided into improved and unimproved groups according to the combination of criteria. The unimproved group included those patients who exhibited improvement before but not after surgery, those who failed to improve after operation, and three who had late deaths related to heart disease.

Results

1. *Operative Mortality:* Causes of death were analyzed with respect to errors in diagnosis or treatment, and those ascribed to complications of mitral stenosis (table 2). A summary of each operative death is presented in the Appendix. Five of the 46 patients in the UW group died within nine days of operation, a mortality of 11%.† Four similar deaths in 14

* It is stressed that the first rather than the last preoperative examination was used for the initial evaluation in operated patients.

† One operative death and four survivors were not included because of failure to satisfy the criteria for selection. Corrected for these omissions, early (operative) mortality was 12% of the UW group.

TABLE 2

Causes of Operative Deaths

Group of Patients	"UW"	"Other"
Number of Patients	5	4
Medical Diagnosis		
Predominant mitral insufficiency	2	1
Surgical Technic and Limitations		
Pulmonary vein approach	1	0
Perforation of atrium	0	1
Ligation of coronary artery	0	1
Inadequate commissurotomy	3	1
Postoperative Management and Pathologic Complications		
Dehydration, Saline infusion (For control of postoperative hyponatremia)	1, 2	0, 0
Early ambulation, atrial fibrillation and bronchial obstruction	1	0
Pulmonary embolism	1	0
Thrombosis of left atrium	1	1

patients in the other group represented a mortality of 29%.* In the nine operative deaths there were errors in medical diagnosis in three, limitations and errors in surgical technic in seven, and errors in postoperative management with complications in eight. Since the incidence of many of these factors has been reduced with subsequent experience with similar case material, several deaths were probably preventable. Furthermore, not all were related to surgical factors, but reflected the importance of errors in management in seriously ill, poor-risk patients.

2. *Clinical Status of Disability in Survivors:* Improvement according to various criteria in operated and unoperated groups is shown in table 3. Incidence of improvement was highest for patient's opinion and lowest for functional capacity, the latter based upon severity of symptoms as described

TABLE 3

Improvement in Early Survivors

	Unoperated			Operated		
	Contra-indicated	Refused	Total	"UW"	"Other"	Total
Number of Patients	11	3	14	41	10	51
Criteria for Improvement						
Patient's opinion	4	0	4	33	6	39
Functional capacity	3	0	3	28	5	33
M.D.'s opinion	3	0	3	31	5	36
Exercise tolerance	4	0	4	31	7	38
Combination of criteria	2	0	2	28	6	34

* Data are not available to evaluate entire experience of these other surgeons with respect to operative mortality.

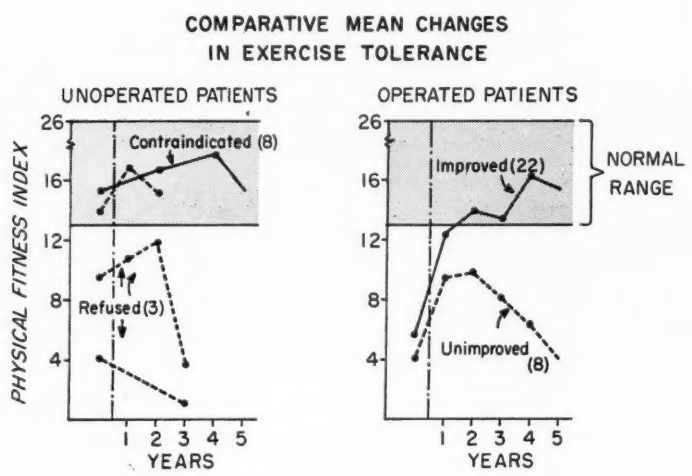

FIG. 1.

by the patient. Agreement among different criteria was not so close as similarity of numbers suggests. Improvement by all criteria occurred in 25 of the UW group and in five of the other group.

Improvement based on the combination of criteria occurred in only two (18%) of 11 patients in whom operation was contraindicated, and in none of three patients who refused operation. In contrast, improvement (by combined criteria) occurred in 28 (68%) of 41 survivors of operation in the UW group, and in six (60%) of 10 in the other group.

3. *Serial Changes in Exercise Tolerance:* Changes in mean exercise tolerance expressed in terms of physical fitness index (PFI) in all patients who were followed into the fourth and fifth years are shown in figure 1. Of patients with contraindications to surgery on initial evaluation, eight showed no significant change and remained in the normal range (figure 1). Individual test scores for the three patients who refused operation are also shown. Two of the latter exhibited deterioration in the third year, whereas the third patient was unchanged at the end of two years.

Serial tests in 30 operated patients showed considerable initial improvement, bringing the mean value up to the lower limits of normal tolerance. In retrospect they were subdivided as "improved" or "unimproved," according to combination of criteria (figure 1). Mean scores of the 22 "improved" patients remained within normal limits after the first year, whereas those of the eight "unimproved" cases showed an initial increase, followed by a decline after two years. Although three of these eight unimproved patients showed no early improvement following operation, the remaining five improved their tolerance for exercise for periods ranging from one to

four years before deterioration. Of these five, hemiparesis secondary to cerebral embolism caused abrupt decrease in tolerance in two. Carditis and progression of mitral regurgitation were suspected clinically in the remaining three. Persistent systemic hypertension also occurred postoperatively in one of these. Four years after initial operation, and following ligation of the inferior vena cava, a second commissurotomy failed to improve chronic congestive heart failure in another.

4. *Adverse Prognostic Factors in Selection for Operation:* Table 4 summarizes the eight factors appearing to be best correlated with operative mortality and results. The first five factors (excluding PFI, pulmonary artery pressure, and jet at operation) are all apparent on clinical evaluation, including a test of exercise tolerance. The latter may be simplified, for this purpose, to the duration of time that effort can be continued.

A higher operative mortality in the UW group was associated with greater age, louder murmur of mitral insufficiency, larger left atrium and greater calcification of the valve at fluoroscopy, reduced endurance and PFI on exercise, increased pulmonary artery pressure and resistance and, finally, palpation of a definite regurgitant jet at surgery. Operative mortality was not related to estimation of functional capacity, atrial fibrillation, or the surgeon's evaluation of the operative procedure or degree of residual stenosis. In the smaller number of patients in the other group, only age and valvular calcification differed with respect to mortality experience. Except for the one accidental death (No. 36, hemorrhage from auricular tear), these other fatal cases also showed a reduced endurance and PFI score and higher incidence of atrial fibrillation. Catheterization data and operative findings did not differ.

In patients surviving operation, failure to improve was associated with greater age, louder murmur of mitral insufficiency, larger left atrium and greater calcification of the mitral valve at fluoroscopy, lower mean pulmonary artery pressure, and stronger jet palpable at surgery. Patients failing to improve in the other group also had louder murmur of mitral insufficiency, greater valve calcification, decreased total pulmonary resistance and stronger jet at surgery.

Mean characteristics of all patient groups studied are indicated in table 6 of the Appendix.

Discussion

Assessment of improvement in survivors of mitral commissurotomy requires, first of all, a definition of improvement. Since discrepancies between severity of symptoms and the objective results of an exercise tolerance test have been demonstrated in this laboratory, care is required for accurate evaluation of disability.[4] Many reports have also indicated differences between subjective evaluation of improvement and objective findings, e.g., reduction in heart size, or incidence of atrial fibrillation.[5-7] For these reasons

TABLE 4

Importance of Adverse Factors in "UW" Patients

Adverse Factor	Operative Mortality	Improvement in Survivors
Age		
>44 years	21%	36%
<45 years	6%	80%
Murmur mitral insufficiency		
>Grade 1 (definite)	23%	59%
<Grade 2	0	74%
Left atrial enlargement (fluoroscopy)		
>Grade 1 (definite)	14%	58%
<Grade 2	5%	81%
Valve calcification (fluoroscopy)		
>Grade 1 (definite)	25%	50%
<Grade 2	9%	77%
Endurance on exercise test		
>4 minutes	26%	71%
<4 minutes	0	67%
PFI score		
>3	25%	73%
<3	0	65%
Pulmonary artery pressure (mean)		
>39 mm. Hg (hypertension)	27%	82%
<40 mm. Hg	6%	59%
Palpable jet at surgery		
>1 (definite)	33%	50%
<2	6%	71%

the three subjective criteria and one objective criterion indicated were used in the present study. Variations within these four criteria occurred in 13 (27%) of the 48 operative survivors seen at final evaluation. Consideration of individual patients suggested the following reasons for such discrepancies:

1. Changing attitudes and motivation on the part of the patient (and possibly of the physician).

2. Improvement in symptoms of pulmonary congestion, but occurrence of disabling embolic complications.

3. Inability to describe slight or moderate improvement by accepted groups of functional capacity, especially when the usual level of "ordinary activities" was limited.

4. Difficulties of measuring exercise tolerance in the presence of either anxiety reaction or abnormal degrees of bradycardia produced by digitalis in patients with atrial fibrillation.

Furthermore, improvement noted following operation by any or all of these criteria need not be attributable to surgical care alone. Attention has been brought to both the fluctuating course of disability in some patients with mitral stenosis treated by medical measures only,[8] and the intensive medical treatment usually necessitated by surgical care. Thus, in the present study, serial exercise tests indicated that improvement occurred only preoperatively in five (15%) of the 33 patients who survived from two to five years. Thus, critical evaluation of improvement attributable to surgery necessitates consideration of discrepancies between subjective and objective changes postoperatively, and must take account of improvement during medical management before operation. For this reason the combination of criteria, as defined, was necessary. It is acknowledged that this in no way evaluates the importance of specific medical care following surgery.

In the present study, operative and late deaths in seven of 46 UW patients resulted in a total mortality of 15%. Improvement following operation occurred in 28 (68%) of 41 survivors. These results are similar to reports of others (table 5).

Best appraisal of the role of surgery in these results requires comparison with comparable unoperated patients. Experience cited in this report is insufficient for such comparisons, although none of the three patients who refused operation improved during follow-up, and two deteriorated.

Since a suitable control group was lacking, appraisal of surgical benefit was made by comparison with available reports of long-term follow-up of nonoperated patients. In Grant's 10-year follow-up of 238 World War I veterans with isolated mitral stenosis, improvement was not even considered as a category.[10] Follow-up study classified patients as unchanged, progressed, or dead. Forty-five per cent of patients with "poor" exercise tolerance, as determined by history and simple exercise tests and approximating class III functional capacity, had died, and 55% of the survivors had shown progression of their disease within 10 years. All of those in the "congested" category (approximating class IV) had died. Likewise, in Olesen's study of 271 patients with predominant mitral stenosis who were followed on an average of 12 years there was no "improved" category.[11] A 10-year follow-up of class III patients showed that 54% had died and 35% of survivors had shown deterioration, whereas all class IV patients had died. In Harken's report of 19 group IV unoperated patients, 17 (90%) died within one year, all but two deaths occurring in less than six months.[12]

Such long-term follow-up studies indicate a high mortality and progression of disability in unoperated patients who were moderately or severely ill on initial evaluation. It is appreciated that patients in these unoperated series might have benefited from improvements in present-day technics of medical management, especially in control of infections. Nevertheless, knowledge gained from these prolonged studies of large numbers of patients

seems superior to individual case reports in evaluating the prognosis of unoperated patients.

Comparison of these operated and unoperated series with respect to longevity is still not feasible, due to differences in duration of follow-up (table 5). When this comparison is restricted to class IV patients only, operation increases longevity. In addition, the improvement noted in about two thirds of survivors in the surgical series suggests a definite alteration of the natural history of disability.

Course of improvement after operation, as evaluated by serial exercise tests, indicated that the improved tolerance apparent in the first year was sustained, with little change, into the fourth and fifth years in many patients (figure 1). On the other hand, eight patients survived four or five years after operation and were classified as unimproved on final examination. However, serial exercise tests indicated a period of temporary improvement postoperatively in five (63%) of these patients. Thus commissurotomy may well have been considered by some to be a worth while palliative treatment for these particular patients.

Estimation of prognosis after mitral commissurotomy should account for both expected mortality and beneficial effects in survivors of the operation. It is likely to be largely dependent upon factors reflecting the general health status of the patient, the specific valvular pathology and its complications, the limitations of a "blind" surgical treatment, and subsequent complications and problems in medical management.

Chronologic age is an important prognostic factor (table 4). Of patients under 45 years of age, 6% died as a result of the operation and 80% of the survivors were improved. By contrast, in patients over 44 years of age, operative mortality was 21%, and only 36% of survivors were improved.

Various manifestations of mitral valve disease were also important prognostic factors (table 4). Thus, an apical systolic murmur, enlarged left atrium, and calcified valve were associated with higher operative mortality and lower incidence of improvement in survivors. The most important

TABLE 5

Comparative Results of Other Surgical Experience

Author	Number of Cases	Follow-up Period	Criteria of Improvement	Mortality		Improvement in Survivors
				Operative	Total	
Ellis[5]	500	½–5 years	Questionnaires, some examinations	12%	15%	63%
Bailey[9]	1000	to 7 years	Not stated	8%	13%	90%
Janton[6]	50	4½–7 years	MD's opinion	6%	18%	73%
"UW" Series	46	2–5 years	Combination of criteria	11%	15%	68%

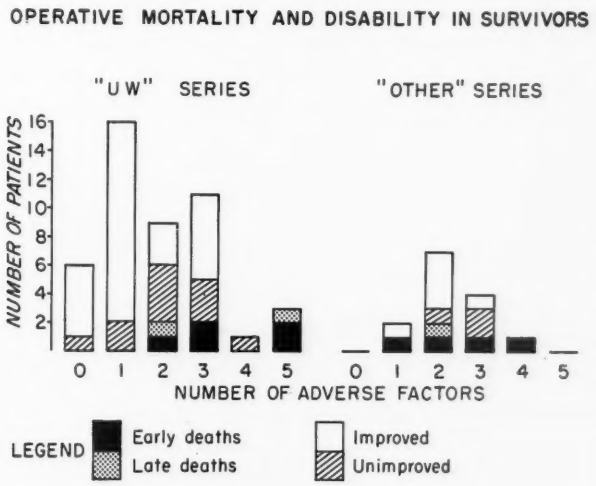

FIG. 2.

prognostic sign, a palpable jet of mitral regurgitation, could not be determined until the heart was explored surgically.

Pulmonary hypertension was associated with both a higher operative mortality and a slightly higher incidence of improvement in survivors (table 4). Test of exercise tolerance was important in predicting the operative risk. This tolerance could be evaluated very simply as duration of endurance for standardized grade walking (which increased oxygen consumption about fourfold). None of the patients who walked for more than four minutes died (except for one who succumbed, due to faulty technic, in the "other" group of patients), in contrast to 26% mortality for those who were unable to walk for four minutes. Failure to improve such poor endurance in those patients who received intensive medical treatment preoperatively constituted an even more important adverse prognostic factor for operative mortality. Duration of effort afforded no reliable prediction of the outcome in survivors, however. Other studies now in progress indicate that patients who are unable to continue this effort for four minutes usually have a fall, rather than a rise, in stroke volume with exercise.[13]

By utilization of the five adverse factors which can readily be determined clinically, it may be possible to predict both operative risk and chances for improvement in patients with mitral stenosis (figure 2). These factors are: age over 44 years, definite apical systolic murmur, definite left atrial enlargement, definite valvular calcification and definite impairment in exercise tolerance.* The data in the present study, combining the "UW" and

* The latter may be simplified to the inability to step up and down on the examining table step at the rate of 20 steps per minute for four minutes. This procedure increases oxygen consumption to the same level as that required by the treadmill test.

"other" patients, indicate an operative mortality increasing from 0 to 67% as the number of these factors present on initial examination increased from 0 to five. It should be noted that none of the patients with less than two adverse factors failed to survive operation (except for the technical error in patient No. 36 in the "other" group). Similarly, incidence of improvement in survivors decreased from 83 to 42% as the number of adverse factors increased from 0 to two or three. Since only five patients with four or five adverse factors were submitted to surgery, there were too few of these cases to state that no improvement would be the invariable result in patients who survived the operation.

It was of further interest to note that none of the unoperated patients who presented less than three of these adverse factors on initial examination has died within the period of this follow-up evaluation. Two patients considered to have contraindications to surgery had three or more adverse factors initially, and both have succumbed from their disease.

It should be emphasized, however, that selection of patients with respect to these five adverse factors represents an oversimplification of a complex problem. Other factors, such as rapid ventricular rate with atrial fibrillation or electrocardiographic evidence of right heart strain, may be important in occasional patients and influence results in groups of patients. Similarly, the success of the surgeon in opening the stenotic valve without producing or aggravating mitral regurgitation, and freedom from serious postoperative complications, affect results of operation.

This simplification emphasizes factors that are both easily determined and likely to be important in every patient. Such prognostic guides may well be of value to the physician who must make a decision regarding commissurotomy in patients disabled by mitral stenosis.

Summary and Conclusions

1. Mortality and disability experience has been evaluated from two to five years after mitral commissurotomy in 60 patients with predominant and symptomatic mitral stenosis. In addition, parallel observations have been made on 11 patients with contraindications to operation, and on three patients who refused operation.

2. Operative mortality varied from 11% to 29%, according to selection of patients and surgeons, and total mortality to date for the operated patients is 15%.

3. Incidence of improvement varied with different criteria of disability. Thirty-four (67%) of 51 survivors of operations exhibited improvement after operation. Improvement was sustained to the time of the last evaluation. In contrast, there was virtually no long term improvement in either this or other studies of unoperated patients.

4. Serial tests of exercise tolerance before and after operation indicated

that improvement in five patients was limited to the preoperative period. Such tests also indicated sustained improvement in 22 (73%) of 30 patients followed into the fourth or fifth year after operation.

5. Adverse factors of prognostic value, present in initial clinical evaluation and determined in retrospect, were: age over 44 years, definite murmur of mitral insufficiency, definite left atrial enlargement and valvular calcification at fluoroscopy, and inability of the patient to walk more than four minutes on a standardized exercise test. Palpation of a definite jet of mitral regurgitation was the most important surgical observation of adverse prognostic value.

It is concluded that mitral commissurotomy had favorably altered the natural history of disability in the majority of patients, and improvement was usually sustained. Factors increasing operative mortality were those relating to severe disability and associated significant mitral insufficiency. Prognosis in survivors of operation was affected more by adverse factors associated with valvular pathology than by severity of initial disability.

Case Reports

UW Series

Case 37. A 45 year old white female developed intermittent hypotension, tachycardia and hyperthermia postoperatively and died on the seventh day. Autopsy showed a pedunculated ball valve thrombus in the left atrium which occluded the mitral orifice. Total fluids had been restricted to 0.5 L. per day during study for prevention of postoperative hyponatremia.[15] Death was attributed, in part, to this dehydration, which is now recognized as excessive.

Case 39. A 30 year old white female had hypotension during operation and developed hyponatremia. Daily saline infusion, also under study in postoperative hyponatremia, led to metabolic acidosis and acute pulmonary edema on the sixth day.[15]

Case 40. A 48 year old white female with chronic productive bronchitis was treated with antibiotics for three months during hospitalization prior to operation. Sputum productivity decreased but did not clear. Early ambulation postoperatively was followed by paroxysmal auricular fibrillation with tachycardia and pulmonary congestion. Abrupt deterioration occurred, with inability to raise secretions, and death followed on the sixth day. Autopsy demonstrated obstructive bronchitis.

Case 45. A 55 year old white female had a calcified thrombus occluding the left atrial appendage. Entry through a left pulmonary vein required occlusion of the left pulmonary artery. Hypotension followed, unrelieved by blood transfusion, and ventricular fibrillation and death ensued. Subsequent experience has indicated such an approach to be unnecessary.

Case 81. A 39 year old male, thought clinically to have predominant stenosis, had findings of predominant regurgitation at operation. Hyponatremia and edema occurred postoperatively. He was given saline infusion and died on the ninth day. Autopsy showed recent pulmonary emboli and infarction.

TABLE 6—Mean Characteristics of All Patient Groups Studied

	Unoperated				Operated											
					Op. Mortality				Late Results							
					"UW"		"Other"		"UW"				"Other"			
	Contraindicated		Refused						Improved		Unimproved		Improved		Unimproved	
	Initial	Final	Initial	Final	Deaths	Survivors	Deaths	Survivors	Initial	Final	Initial	Final	Initial	Final	Initial	Final
Number	11		3		5	41	4	10	28	28	13	13	6	6	4	4
Females	91%		33%		80%	76%	75%	50%	75%		77%		50%		50%	
Age average	39		34		44	39	49	38	36		43		39		36	
Range	25–52		19–50		30–55	19–65	44–55	25–47	19–57		20–65		25–47		26–44	
Symptoms-duration (MDN)	6		6		10	5	10	8	5		3		6		10	
Precipitating factors																
None	9–82%		2–67%		4–80%	31–76%	4–100%	10–100%	23–80%		8–62%		6–100%		4–100%	
Pregnancy	1					3			2		1					
Overwork	1		1													
Resp. infection					1	2					2					
Pulm. embolism						3			2		1					
Art. embolism						2			1		1					
Severity—Fatigue	1.6	1.5	1.5*	2.5*	2.4	2.4	2.3	2.1	2.5	1.3	2.3	1.8	2.2	0.7	2.0	1.0
Dyspnea	1.3	1.2	2.0*	2.5*	2.4	2.3	2.5	2.6	2.1	0.9	2.6	1.9	2.7	0.7	2.5	2.0
Orthopnea	0.5	0.4	1.0*	2.0*	1.4	1.2	1.5	1.1	1.0	0.1	1.7	1.1	1.2	0.7	1.0	0.8
Edema	0.4	0.5	0.5*	1.0*	1.4	0.7	0.5	0.7	0.6	0.3	0.7	0.6	0.8	0.3	0.5	1.0
Functional classification																
II	7	10	1		20%	10%		10%	7%		15%		17%		0	
III	4	1	2	2	60%	71%	75%	80%	71%		70%		66%		100%	
IV				1	20%	19%	25%	10%	22%		15%		17%		0	
Mean	2.4	2.1	2.7	3.3	3.0	3.1	3.3	3.0	3.1		3.0		3.0		3.0	
Murmur intensity (0–6)																
MS	2.5	2.7	3.5*	4.0*	2.2	3.0	2.8	2.7	3.1	2.4	2.9	2.3	2.3	2.3	3.3	2.8
MI	0.5	0.5	1.5*	2.0*	2.2	1.0	1.5	1.3	0.9	1.0	1.5	1.9	0.3	0.7	2.8	3.3
Fluoroscopy (0–3)																
None																
Left atrium	1.0	1.1	2.0	2.0*	1.8	1.5	1.5	1.6	1.4	1.1	1.8	1.8	1.7	1.3	1.5	2.3
Mitral calcium	0	0.2	0	0*	1.0	0.5	0	0.6	0.4	0.6	0.8	1.1	0.5	1.0	0.8	1.8
EKG																
NSR	73%	55%	50%*	50%*	60%	51%	0	70%	50%	46%	54%	30%	67%	50%	75%	25%
RHS prob.-def.	18%	9%	50%*	50%*	80%	32%	50%	50%	32%		31%		33%		75%	
Exercise tests																
Endurance	9.1	9.5	10.0	5.2	2.2	5.8	3.5‡	3.6	5.8	9.7	6.1	7.4	3.3	8.8	3.5	5.5
PFI	13.5	15.4	8.9	6.7	1.8	6.3	2.5‡	3.8	6.0		6.9		3.7		3.8	
Cardiac catheterization																
PAP mean					51[5]†	43[28]†	42[2]†	46[8]†	45[19]†		35[9]†		45[4]†		48[4]†	
TPR					1300[4]	827[27]	907[2]	982[8]	880[18]		722[9]		1255[4]		707[4]	
Operative findings (0–3)																
Stenosis, initial					3.0	2.8	2.8	2.8	2.9		2.5		3.0		2.8	
Stenosis, final					1.4	1.2		0.9	1.3		0.9		0.8		1.0	
Jet, initial					1.2	0.5	1.2	1.2	0.4		0.6		0.7		2.3	
Jet, final					1.0	0.5		1.3	0.4		0.5		1.2		1.7	
Procedure																
Dilatation					60%	33%	25%	0	41%		15%		0		0	
Commissurotomy					40%	67%	75%	100%	59%		85%		100%		100%	

* 2 Patients seen at both initial and final. † Superscript indicates number of patients studied.
‡ Endurance 1.3, PFI 0.9 without patient No. 36, accidental death at operation.

Other Series

Case 36. A 55 year old white female had a tear of the posterior wall of the left atrium during commissurotomy. Excessive hemorrhage led to death on the operating table.

Case 38. A 48 year old white female had the left circumflex coronary artery accidentally clamped. Ligation was required because of persistent bleeding and dissection into adjacent myocardium. Heart failure occurred postoperatively and death followed on the seventh day.

Case 44. A 44 year old white female, thought by some to have predominant regurgitation and inadequate cardiac reserve for surgery, underwent operation because of severe and unremitting disability. Regurgitation was the predominant lesion at operation. Death occurred in four days.

Case 82. A 47 year old white male required atrial entry and incision because of thrombus in the appendage. Atrial tear, with hemorrhage, occurred. Although hemorrhage was controlled and blood loss replaced, death occurred on the operating table.

SUMMARIO IN INTERLINGUA

Le incidentia de morte e de invaliditate duo a cinque annos post commissurotomia mitral esseva evalutate in 60 patientes con predominante e symptomatic stenosis mitral. In plus, observationes parallel esseva facite in 11 patientes in qui le operation esseva contraindicate e in tres qui habeva refusate le operation. Le mortalitate operatori variava ab 11 a 29 pro cento, secundo le selection del patientes e secundo le chirurgos, e le mortalitate total inter le patientes operate ha attingite 15 pro cento al tempore presente. Le incidentia de invaliditate inter le superviventes variava con variationes del criterios usate pro evalutar le grado de melioration. Trenta-quatro ex 51 superviventes (67%) exhibiva melioration post le operation. Le melioration se manteneva usque al tempore del plus recente evalutation. Per contrasto con isto, practicamente nulle melioration occurreva in nonoperate patientes, tanto in iste como etiam in altere studios de nonoperate patientes. Tests serial de tolerantia pro exercitio ante e post le operation indicava que le melioration in cinque patientes esseva restringite al periodo preoperatori. Tal tests etiam indicava melioration durative in 22 ex 30 patientes (73%) qui remaneva sub observation usque al quarte o quinte anno post le operation.

Factores adverse in le prognose—presente in le evalutation clinic initial e determinate in retrospecto—esseva: etate de plus que 44 annos, definite murmures de insufficientia mitral, definite allargamento sinistro-atrial e calcification valvular apparente sub fluoroscopia, e incapacitate del patiente de ambular plus que quatro minutas in un standardisate test de exercitio. Palpation indubitose de regurgitation mitral esseva le plus importante observation chirurgic de adverse signification prognostic.

Es concludite que commissurotomia mitral alterava favorabilemente le curso del historia natural del invaliditate in le majoritate del patientes e que le obtention de melioration esseva le regula. Factores que augmentava le mortalitate operatori esseva factores del genere relationate con sever invaliditate e le associate insufficientia mitral de grados significative. Le prognose in superviventes del operation esseva afficite plus per factores adverse associate con pathologia valvular que per le severitate del invaliditate original.

BIBLIOGRAPHY

1. Bruce, R. A., Merendino, K. A., Pampush, J. J., Bergy, G. G., and Broch, L. L.: Functional evaluation of mitral valvulotomy, Am. J. Med. 20: 745, 1956.

2. Levine, S. A., and Harvey, W. P.: Clinical auscultation of the heart, 1950, W. B. Saunders Company, Philadelphia, pp. 145–148.
3. Bruce, R. A.: Evaluation of functional capacity and exercise tolerance of cardiac patients, Mod. Concepts Cardiovas. Dis. **25**: 321, 1956.
4. Bergy, G. G., and Bruce, R. A.: Discrepancies between subjective and objective responses to mitral commissurotomy, New England J. Med. **253**: 887, 1955.
5. Ellis, L. B., and Harken, D. E.: The clinical results in the first five hundred patients with mitral stenosis undergoing valvuloplasty, Circulation **11**: 637, 1955.
6. Jan'n, O. H., Davica, J. C., and Glover, R. P.: Status of fifty patients four and a half to seven years after mitral commissurotomy, Circulation **14**: 175, 1956.
7. Gary, J. E.: Late follow-up study of radiologic changes after mitral valvuloplasty, New England J. Med. **254**: 831, 1956.
8. Soloff, L. A., and Zatuchni, J.: Some difficulties in evaluating functional results after mitral commissurotomy, J. A. M. A. **154**: 673, 1954.
9. Bailey, C. P., and Boulton, H. E.: Criteria for and results of surgery for mitral stenosis, New York State J. Med. **56**: 649, 825, 1956.
10. Grant, R. T.: After histories for ten years of a thousand men suffering from heart disease. A study in prognosis, Heart **16**: 275, 1933.
11. Olesen, K. H.: Mitral stenosis. A follow-up of 351 patients, 1955, Einar Munksgaard's Forlag, Copenhagen.
12. Harken, D. E., Ellis, L. B., Dexter, L., Farrand, R. E., and Dickson, J. F., III: The responsibility of the physician in the selection of patients with mitral stenosis for surgical treatment, Circulation **5**: 349, 1952.
13. Bruce, R. A., Fuller, T. J., Andrus, W. W., and Wiederhielm, C. A.: Unpublished data, 1957.
14. Welch, G. E., Bruce, R. A., Bridges, W. C., Johnson, A. D., Lehmann, J. H., and Neilsen, M.: Comparison of a new step test with a treadmill test for the evaluation of cardiorespiratory working capacity, Am. J. M. Sc. **223**: 607, 1952.
15. Bruce, R. A., Merendino, K. A., Dunning, M. F., Scribner, B. A., Donohue, D., Carlsen, E. R., and Cummins, J.: Observations on hyponatremia following mitral valve surgery, Surg., Gynec. and Obst. **100**: 293, 1955.

CHRONIC SODIUM CHLORIDE TOXICITY: THE PROTECTIVE EFFECT OF ADDED POTASSIUM CHLORIDE *

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EARLY in our investigations of chronic sodium chloride toxicity, possible interrelations between dietary sodium and potassium came to our attention. There has been a good basis for suspecting such since 1843. At that time it was suggested, on the basis of direct chemical analysis, that the herbivores' need for salt and the occasion for their long journeys in search of it were due not to lack of sodium in the diet but to an excess of potassium. We drew attention to this in introductory remarks to our presentations before the September, 1952, meeting of the American Physiological Society.[1, 2] These remarks were subsequently embodied in an editorial in 1954.[3]

It would seem, then, that the greater potassium content of the herbivorous diet rather than its smaller salt content was the reason for the herbivores' great treks to salt licks. Carnivores, on the other hand, apparently acquire the salt they need from their natural diet, i.e., the flesh of other animals.

Unquestionably the finest and greatest of all physiologic experiments was Claude Bernard's with a single rabbit, accomplished all within six weeks. From it flowed the entire concept of endogenous as different from exogenous metabolism. For two weeks he fed the rabbit vegetables. It passed a cloudy alkaline urine. For two weeks he fed the rabbit meat. It passed a clear acid urine. For the final two weeks he fed the rabbit nothing. It passed a clear acid urine. From this he concluded the rabbit was eating meat during that last two weeks. Rabbit meat. Think now also about *fera naturae,* their medical and surgical emergencies.[4] If a saber-toothed tiger (figure 1) encountered a woolly mammoth apt with his tusks he might come out of the affair with a real "Saturday night" set of contusions, lacerations and fractures. He would lie where he fell, or at best nearby where he could crawl. Whether he lived or died would then depend entirely upon the physiologic resources built into him for the emergency by eons of evolution due to

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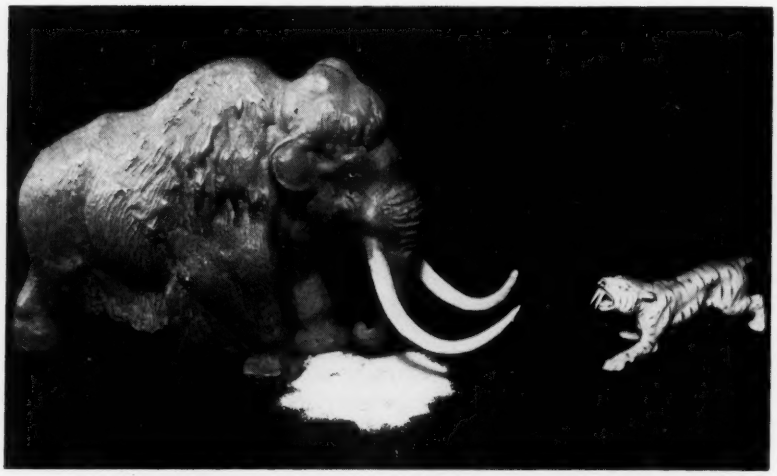

FIG. 1. Woolly mammoth and saber-toothed tiger.

the fact that nursing service was so poor for saber-toothed tigers. While on the one hand he would not be roused from his sleep at five to be bathed, and then wait three hours for breakfast, and thus by some would be considered blessed to die in peace, yet neither would food and water be given to him. He would have to start at once on a diet of saber-toothed tiger meat, and this, mind you, without water. As he digested himself kilogram by kilogram, a growing awareness of a new kind of problem would dawn upon his kidneys. The kidneys, of course, had already successfully handled the immediate problems of the day of the violence, correctly interpreting the abrupt diminution in renal arterial blood pressure as evidence their master's throat had been cut, and so ceasing to form urine or, if the emergency seemed just a little less dire, reducing to the *urine obligatoire* at most. This maneuver, designed of course to save the precious remaining supply of water and salt, together with the tiger meat-eating regimen, soon sets the stage for the new difficulty. With 20 times (more or less) as much potassium in the juices of the cells as in the extracellular water, the kidney must face the tricky matter of dumping potassium to prevent intoxication with this now undesirable catabolite, while simultaneously holding tenaciously to its needed and dwindling supply of water and sodium. How well advised it would be to enlist the aid of that yellowish body above it, asking for a copious supply of aldosterone to aid it in its difficult and vital task.

This anecdote is not mere whimsy. Armchair philosophy may have its drawbacks, and teleologic reasoning is always false, but it certainly is not foolish and it does not seem false to suggest that, while there is important survival value in an ability on the part of the terrestrial animal kingdom to

conserve sodium chloride and water in times of emergency, there is no evident circumstance among wild animals requiring conservation of potassium. Indeed, the reverse must be the case. Whether the animal obtained sustenance from the world around it or from the tissues of its own body, whatever else may have been lacking, there was no dearth of potassium. Rather, in most situations, there was an embarrassment of this particular riches. While herbivores do indeed go to salt licks—and this might serve as an excuse for a salt cellar on every table—no animal but the human extracts the potassium from its food by boiling it in water and throwing the water away. A legacy of evolution is an embarrassingly good mechanism for water and salt retention which is excellently efficient for excess potassium excretion. The lack, however, of a potassium-conserving mechanism, together with our propensity for discarding cooking liquids, may well have all of us, or most of us, in or near potassium deficiency. That potassium is an effective antagonist to the toxic action of sodium chloride will be clearly evident from the data below. It remains a speculation that potassium deficiency may be a real threat to human health. An adequate supply of it is life-ensuring for the salt-eating rat.

Potassium as possibly prophylactic or therapeutic in human disease is not a new thought either. Priddle in the Canadian literature [5] advocated it for hypertension in 1943. The observations of McQuarrie are especially relevant to the present discussion. These fine reports in the early 1930's illustrate the hypertension-governing effects of potassium chloride added to high sodium chloride diets in "salt-eating" children (one as much as 64 gm. daily) : "In the case of one normal control subject, the ingestion of 15 gm. of sodium chloride every six hours caused an increase in blood pressure from 115/80 to 148/100 mm./Hg, when the subject was on the simple, relatively low-potassium diet given to the three diabetic children, but little or no change when he was taking an ordinary mixed diet containing liberal amounts of vegetables and meats." [2]

Our investigations of the chronic effects of high levels of dietary sodium chloride in the rat [1, 3, 6–14] were initiated in 1951. Impairment of growth, the occurrence of hypertension, electrocardiographic evidences of cardiac damage, hypercholesteremia, alterations in sodium space, decreased survival, varying degrees of hypertrophy of the heart, kidneys and adrenals, and pathologic changes in the small vessels and kidneys were, in general, proportional to the salt intake levels. A small percentage (15%) of the rats eating high levels of sodium chloride (in excess of 7.0%) developed massive edema and a clinical syndrome resembling nephrosis. The findings of associated hypertension and renal and vascular lesions were presented before the College in 1953, and at that time we reported that experiments feeding added potassium chloride were under way. We feel advised to continue each experiment throughout the rats' life span, as the deleterious effects on survival of the

lower levels of added sodium chloride are not evidenced until some 16 months (approximating late middle age for man) on the regimen, although the systolic blood pressure is elevated from the sixth month.

Material and Methods

Six hundred twenty-two young male Sprague-Dawley rats were housed in humidity-controlled, constant temperature quarters with free access to food and demineralized water. The basic ration from which the diets were derived contained 25.1% vitamin-test casein, 51.8% cane sugar, 20.0% hydrogenated vegetable fat, 2.9% reagent grade minerals (the Hubbel, Mandel and Wakeman mix), and 0.2% crystalline vitamins. In the first experiment, 30 rats were assigned to each dietary group. The control diet contained 0.15% sodium chloride. The other six groups were fed 2.8, 5.6, 7.0,

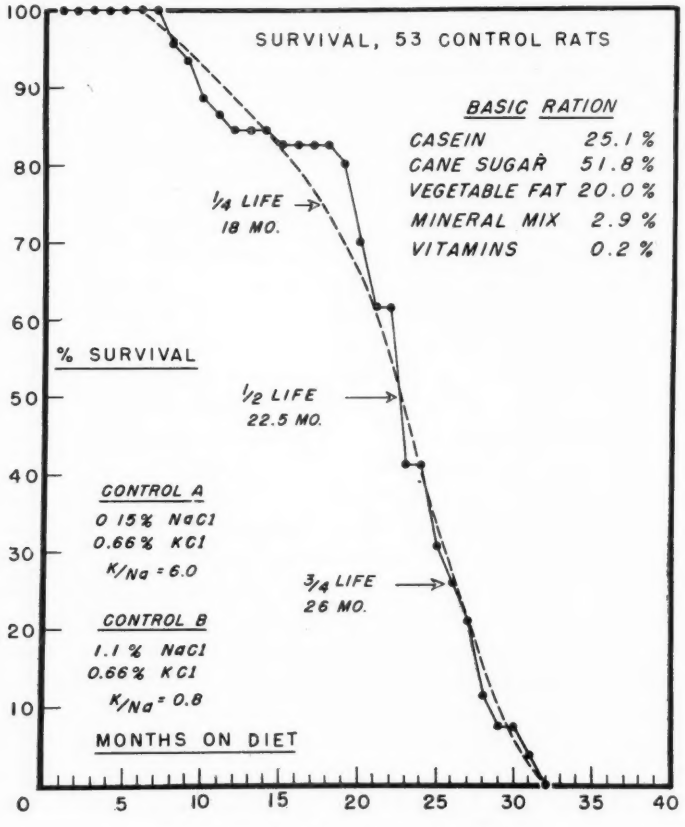

Fig. 2. Survival curves on control diets.

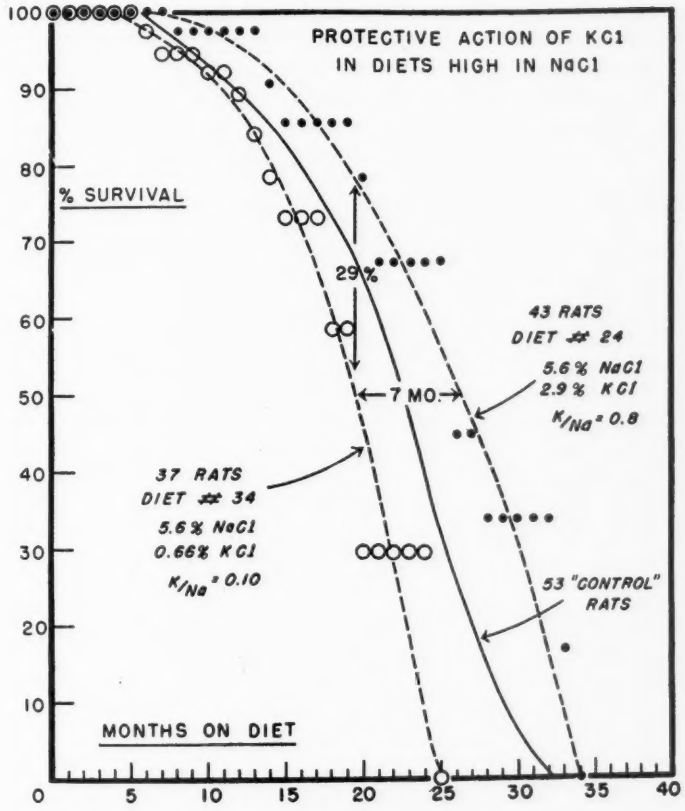

FIG. 3. Survival curves, 5.6% sodium chloride—2.9% potassium chloride, 5.6% sodium chloride—0.66% potassium chloride, and control diets.

8.4 and 9.8% sodium chloride. Later experiments included the feeding of 1.1% and 2.0% sodium chloride as control diets, and 14.0% and 21.0% sodium chloride as very high salt diets. For the exploration of the effect of bringing the potassium : sodium ratio toward one, 43 control rats were fed 1.1% sodium chloride (potassium/sodium = 0.8). The added salt diets contained 5.6% sodium chloride with 0.66 and 2.9% potassium chloride, 8.4% sodium chloride with 0.66 and 4.7% potassium chloride, and 9.8% sodium chloride with 0.66 and 5.6% potassium chloride. There were 43 rats on each of the elevated salt diets with added potassium chloride except the 9.8% sodium chloride—5.6% potassium chloride level which was fed 30 animals. Thirty-seven rats were concurrently eating 5.6 and 8.4% sodium chloride, while 30 comprised the 9.8% sodium chloride group.

Observations in the pilot potassium chloride experiment (53 rats) and

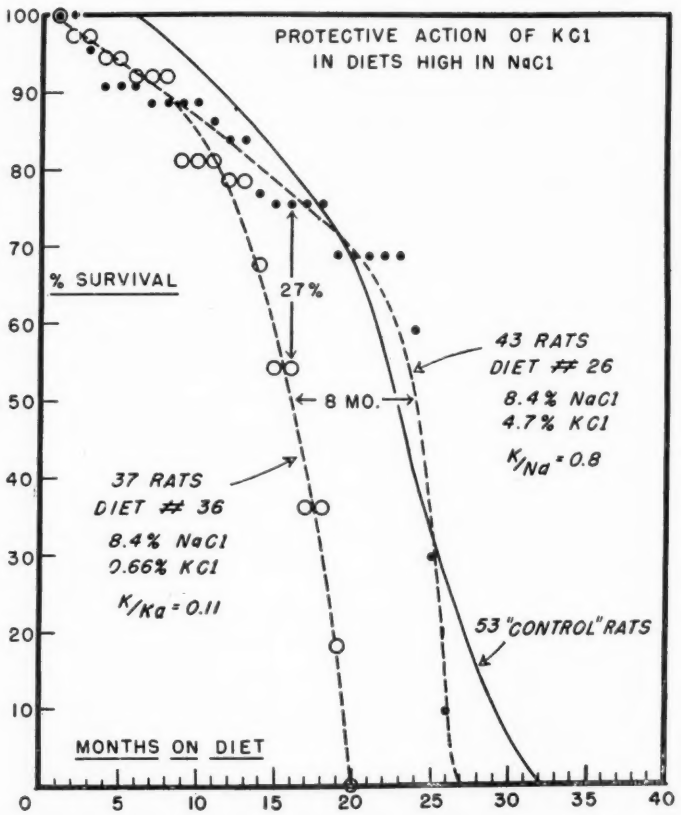

FIG. 4. Survival curves, 8.4% sodium chloride—4.7% potassium chloride, 8.4% sodium chloride—0.66% potassium chloride, and control diets.

the later experiment (106 rats), were frequently combined, and in some facets findings on all 622 rats were included for analysis, as the first experiment has proved remarkably reproducible. The experimental regimen and methods have been fully described elsewhere.[7, 8, 9, 14]

RESULTS

Survival: The control rats on the added potassium chloride experiment (Control A, figure 2) followed the expected survival curve, reaching the 50 and 75% survival points at times almost identical to those of the control rats in earlier experiments. Half of the rats eating the control ration live 22.5 months. Adding 2.9% potassium chloride to diets containing 5.6% sodium chloride increased the 50% (figure 3) survival time some seven months (ap-

proximately 21 years for man). These potassium-protected rats outlived the controls, posing the question that the control diet may be suboptimal for potassium. Half of the rats eating 8.4% sodium chloride with 4.7% potassium chloride survived eight months (about 24 years in man) longer than their counterparts (figure 4). There was a high incidence of the early nephrotic syndrome among the rats eating 9.8% sodium chloride with 5.6% potassium chloride. Those rats surviving this critical two- to four-month period paralleled the controls for the ensuing 10 months and, from the eleventh month, larger percentages of their original group were surviving than of their counterparts eating 9.8% sodium chloride.

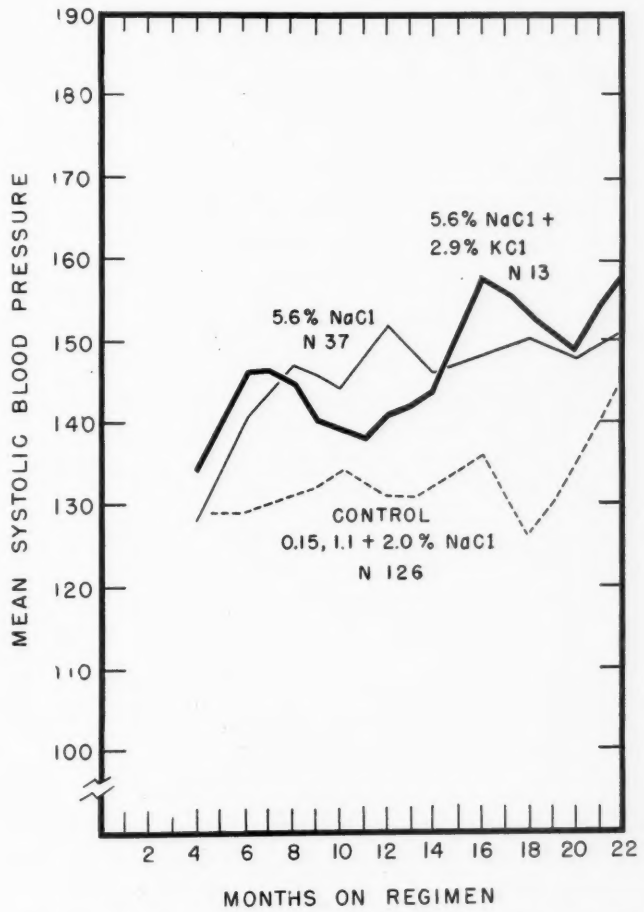

FIG. 5. Mean systolic blood pressure at 5.6% sodium chloride levels, with and without added potassium chloride.

Hypertension: There was no apparent effect of added potassium chloride on the modest hypertension of lower levels (5.6%) of added dietary salt (figure 5). Extra potassium chloride lowered the *high* hypertension accompanying high sodium chloride (8.4 and 9.8%) feeding to intermediate levels (figure 6) for a prolonged period—from eight to 20 months.

Radioactive Sodium 24: In the total exchangeable sodium measurements at 8 to 10 months (figure 7), the 5.6% sodium chloride groups, with or without added potassium chloride, were similar to each other and to the two control groups. At levels of 8.4 and 9.8% sodium chloride the blocking

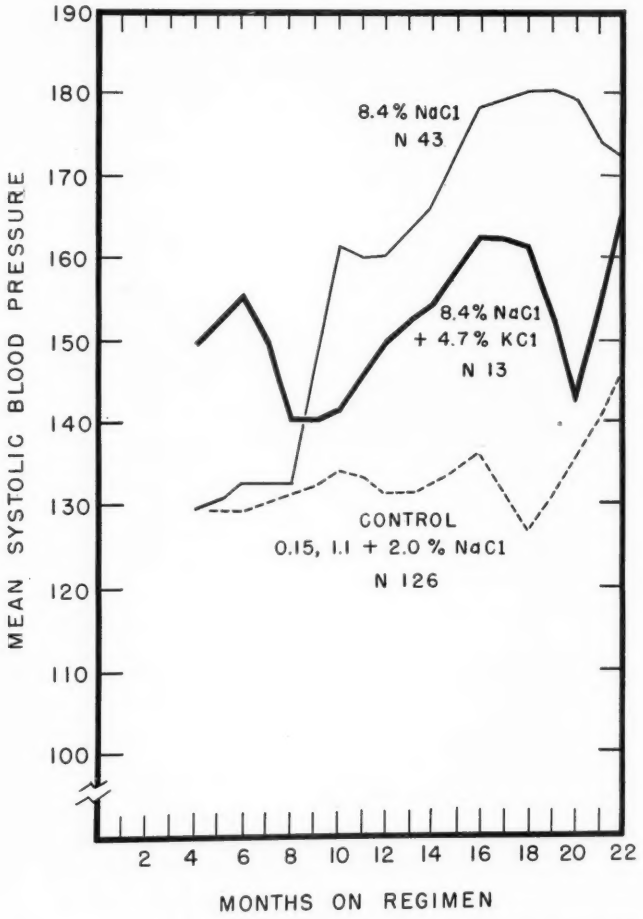

FIG. 6. Mean systolic blood pressures at 8.4% sodium chloride levels, with and without added potassium chloride.

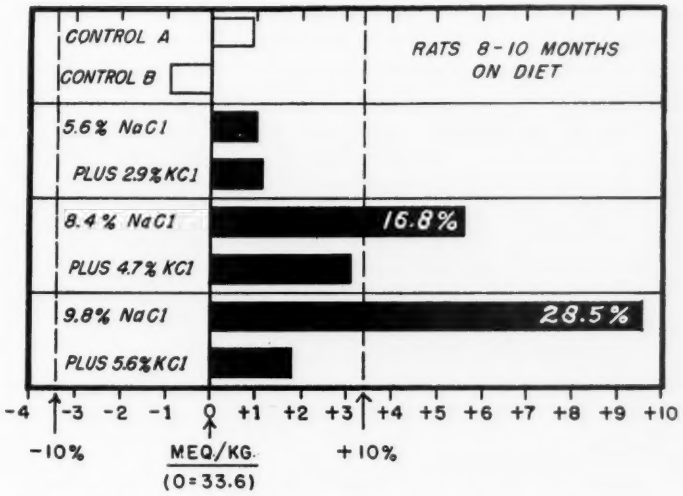

FIG. 7. Exchangeable sodium determined by method of isotope dilution using Radioactive Sodium 24. (The chemical sodium was measured by flame photometry using the Coleman Instruments, Inc., Model 21 flame photometer.)

effect of potassium chloride was marked. At the 5.6% sodium chloride level the added potassium chloride did not exhibit blocking effects in the total exchangeable sodium or systolic blood pressure, although the protection afforded survival was significant. At the 8.4% sodium chloride and 9.8% sodium chloride levels the blocking effects of added potassium chloride in the total exchangeable sodium were also reflected in the lowering of *high* hypertension measured after the same period 8 to 10 months on the experimental regimen.

DISCUSSION

It is evident that there are at least two kinds of hypertension among rats eating excessive sodium chloride. The first, seen at the 2.8 and 5.6% sodium chloride level, is similar in degree and clinical course to that of human "benign essential hypertension." There is no associated excess total body sodium, and it is not altered by increased potassium chloride intake, although the latter does greatly increase the average survival time. At higher levels of salt feeding (8.6 and 9.8%) there is a further elevation of blood pressure and there is an elevated total body sodium. Added potassium chloride in this situation lowers the blood pressure but only to the intermediate level seen at lower levels of high salt feeding with or without added potassium. It prevents the elevation of total body sodium and it also greatly enhances

survival. These observations may account for some of the confusion in the literature as to whether potassium is or is not effective in human hypertension. Our data suggest protection in the form associated with total body sodium excess, and then only to reduce blood pressure to intermediate levels. It is probable that a search would reveal the existence of human counterparts to these two sorts of high salt hypertension seen in our rats. We intend to begin such a search and hope that others will do so too. There are doubtless other badges by which these two kinds of hypertension may be known—perhaps the steroid pattern could give a clue. While no direct causal relation is demonstrated between high hypertension and excess total body sodium, the association is strong, and one cannot well resist the temptation to link them in a working hypothesis, as have others from different kinds of data.[14]

The great prolongation of life brought about by adding potassium at lower levels of high salt feeding cannot be explained on the basis of preventing the "benign essential hypertension" seen among the 2.8 and the 5.6% salt rats. The rationalization offered in the introduction to this presentation appeals to us. At the moment we believe our "control" rats are eating a diet suboptimal in potassium content, and we suspect that humans are not only loading their food with dangerous amounts of sodium chloride but also may concurrently be depriving themselves of potassium. We cannot fail to comment on the implications of the rat experiment. If one were issuing life insurance to rats determined to eat excess salt, it would be well to insist on a concurrent increase in potassium chloride.

SUMMARIO IN INTERLINGUA

In 1953 iste gruppo de autores reportava al Collegio American de Medicos lor observationes in re le effectos del augmentation de chloruro de natrium (commun sal de cocina) como le sol entitate variabile in un dieta que in altere respectos esseva completemente purificate. A ille tempore le autores signalava le possibilitate del existentia de un interrelation inter kalium e natrium e notava le facto que un tal esseva jam postulate in 1843, le anno quando directe analyses chimic demonstrava que le importante differentia que existe inter dietas herbivore e carnivore in le resultante proportion de kalium a natrium es le effecto de un multo plus alte ingestion de kalium per le herbivoros—le sol animales que cerca supplementos de chloruro de natrium a stationes salifere.

Un augmento del chloruro de natrium in le dieta administrate durante lor integre vita a 622 rattos mascule esseva proportionalmente associate con crescentia defective, hypertension, hypercholesteremia, edema, insufficientia renal e cardiac, augmento del spatio de natrium radioactive, anormalitates electrocardiographic, acceleration del mortalitate, e extense arteriosclerosis. Studios destinate a explorar le effecto del addition de chloruro de kalium a dietas ric in chloruro de natrium esseva initiate in 1953. Chloruro de kalium—addite in quantitates sufficiente pro approximar le contentos dietari de kalium e natrium al proportion 1 : 1—representava un remarcabile grado de protection. Le hypertension e su effectos esseva attenuate; le natrium del corpore total remaneva normal; e le superviventia probabile del animales experimental esseva dramaticamente augmentate. Un correspondente augmento del superviventia probabile in humanos amontarea a 20 annos o plus.

Durante que un excesso de sal commun es "dur" pro le rattos, le addition de chloruro de kalium protege le animales contra le effectos toxic del ingestion excessive de chloruro de natrium. Le majoritate del effectos adverse de un augmento del ingestion de chloruro de natrium non se manifesta ante que un tertio del vita normal del rattos ha passate. Le effectos super le superviventia, con nivellos de sal additional correspondente al "estimate consumption dietari de humanos in America," non es apparente ante etates tarde-median, e etiam le effectos protectori de kalium se manifesta solmente a ille tempore.

BIBLIOGRAPHY

1. Meneely, G. R., Tucker, R. G., Darby, W. J., and Auerbach, S. H.: Hypertension, edema and renal failure produced in the rat by high salt diet, Proc. Am. Physiol. Soc., Am. J. Physiol. **171**: 750, 1952.
2. Thompson, H. W., and McQuarrie, I.: Effects of various salts on carbohydrate metabolism and blood pressure in diabetic children, Proc. Soc. Exper. Biol. and Med. **31**: 907, 1933–34.
3. Meneely, G. R.: Salt, Am. J. Med. **16**: 1, 1954.
4. Meneely, G. R.: The relation of sodium to congestive failure, Trans. Am. Coll. Cardiol. **4**: 305, 1954.
5. Priddle, W. W.: Observations on the management of hypertension, Canad. M. A. J. **25**: 5–8, 1931.
6. Meneely, G. R., Tucker, R. G., Auerbach, S. H., and Darby, W. J.: Renal damage in rats fed large quantities of sodium chloride, Proc. Am. Soc. Clin. Invest., J. Clin. Investigation **31**: 650, 1952.
7. Meneely, G. R., Tucker, R. G., and Darby, W. J.: Chronic sodium chloride toxicity in the albino rat. I. Growth on a purified diet containing various levels of sodium chloride, J. Nutrition **48**: 489, 1952.
8. Meneely, G. R., Tucker, R. G., Darby, W. J., and Auerbach, S. H.: Chronic sodium chloride toxicity in the albino rat. II. Occurrence of hypertension and a syndrome of edema and renal failure, J. Exper. Med. **98**: 71, 1953.
9. Meneely, G. R., Tucker, R. G., Darby, W. J., and Auerbach, S. H.: Chronic sodium chloride toxicity: hypertension, renal and vascular lesions, Ann. Int. Med. **39**: 991, 1953.
10. Tucker, R. G., Darby, W. J., Auerbach, S. H., Ball, C. O. T., and Meneely, G. R.: Effect of dietary NaCl on the longevity of the albino rat, XIX, International Physiological Congress, Montreal, abstracts of communications, p. 838, 1953.
11. Meneely, G. R., Lemley-Stone, J., Tucker, R. G., Blake, T. M., Auerbach, S. H., Darby, W. J., and Goodpasture, E. W.: Chronic sodium chloride toxicity: the arteriosclerotic lesion, Proc. Am. Soc. for the Study of Arteriosclerosis, Circulation **12**: 481, 1955.
12. Meneely, G. R., Darby, W. J., Lemley-Stone, J., Tucker, R. G., and Ball, C. O. T.: Survival of rats prolonged by adding potassium chloride to diets containing toxic levels of sodium chloride, Proc. Am. Physiol. Soc., Am. J. Physiol. **187**: 617, 1956.
13. Youmans, J. B.: The chronic toxicity of salt (sodium chloride), The 1956 Jerome Cochran Lecture, Med. Assoc. State of Alabama J. **26**: 161, 1957.
14. Tucker, R. G., Ball, C. O. T., Darby, W. J., Early, W. R., Kory, R. C., Youmans, J. B., and Meneely, G. R.: Chronic sodium chloride toxicity in the albino rat. III. Maturity characteristics, survivorship and organ weights, J. Gerontol. **12**: 182–189 (1957).
15. Tobian, L., Jr.: Tissue cations and water in arterial hypertension, Circulation **5**: 754, 1952.

DIFFERENTIATION OF MACROCYTIC ANEMIAS AND DIAGNOSIS OF PERNICIOUS ANEMIA AND SPRUE IN REMISSION BY ACCELERATED MEASUREMENT OF HEPATIC UPTAKE OF RADIOACTIVE $Co^{60}B_{12}$ *

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THE differential diagnosis of various types of macrocytic anemia often presents difficult clinical problems. Many cases of dietary folic acid or B_{12} deficiency and sprue cannot be distinguished from pernicious anemia by any available criterion. Moreover, very often pernicious anemia in remission or in a nonanemic stage, and the oligosymptomatic sprue, can be diagnosed only tentatively by history, since the clinical and hematologic findings following treatment, including B_{12} levels in blood, may be uninformative.

In all these instances the determination of the presence or absence of Castle's intrinsic factor in the stomach has diagnostic significance, since its secretion is abolished in pernicious anemia [1] but is usually well preserved in all other macrocytic anemias. A unique feature of this abnormality in pernicious anemia is not only that it exists at the onset of the disease and in relapse, but also that it is found after treatment in the remission period. This is due to the persistence of gastric atrophy in pernicious anemia throughout the life of the patient, irrespective of the stage of disease.[2]

Until recently the tests for the presence or absence of intrinsic factor in the stomach required a difficult assay of intrinsic factor activity by repeated counts of reticulocytes and red cells after administration of the tested gastric juice to a patient with pernicious anemia in relapse.[3] With the advent of vitamin B_{12} labeled with radioactive Co^{60}, [4] or, recently, with Co^{58} or Co^{56}, [5] this task has become much easier.

Since intrinsic factor is necessary for the absorption of physiologic

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amounts of vitamin B_{12} from the intestine, the absence of this factor from the stomach impairs intestinal absorption of this vitamin. Therefore, conversely, the determination of the intestinal absorption of vitamin B_{12} permits inferences as to the presence or absence of the intrinsic factor in the stomach, which is diagnostically significant in the differentiation of macrocytic anemias.

The isotope methods available for the measurement of the intestinal absorption of radioactive vitamin B_{12}—i.e., the fecal excretion test,[6] the urinary flushing technic,[7] the measurement of the hepatic uptake of $Co^{60}B_{12}$,[8] and the determination of radioactivity of the serum,[9, 10] following oral administration of a tracer dose of this vitamin—have been currently used also for the determination of the presence or absence of intrinsic factor in the stomach, and for the differential diagnosis of macrocytic anemias.[6-23]

Comparative studies by several groups of investigators have shown that results obtained with these technics are well comparable.[10, 11, 12] All of these technics were applied successfully to the clinical differentiation of macrocytic anemias and to detection of pernicious anemia in remission,[6-23] but each has some advantages and disadvantages which make it more suitable for one purpose or another. The relative merits and drawbacks of these methods are listed in table 1.

In the present paper we shall present a simplified and accelerated modification of the measurement of the hepatic uptake of radioactive B_{12},[41] which we think is more suitable for clinical diagnostic use than the original method [8] and some of the other isotope technics. This will be supported by data indicative of the diagnostic significance of the measurement of the hepatic uptake of radioactive B_{12} for differentiation of types of macrocytic anemia and gastric anacidity, and detection of pernicious anemia and sprue in relapse, in remission and in the preanemic stage.

The measurement of hepatic uptake of radioactive B_{12} [8] is based on the premise that B_{12} absorbed in the intestine is ultimately deposited in the liver. There it can be detected with a sensitive scintillation counter by scanning the cutaneous projections of the liver superficially, following oral administration of a tracer dose of radioactive B_{12} labeled with cobalt ^{60}. The hepatic uptake of radioactive B_{12} can be determined with any available scintillation equipment for external monitoring of the internal organs.[8, 10-12, 29-35] It usually reaches a peak at the end of the first week following the ingestion of the oral tracer dose of radioactive B_{12}.[8, 10, 12]

When a similar dose of radioactive B_{12} is given to patients with pernicious anemia in relapse or remission, none or only traces of this material will be absorbed in the intestine because of the lack of intrinsic factor, and no radioactive material will be deposited in the liver.[8] However, when the same tracer dose is given to the same patient with pernicious anemia, either in relapse or in remission, but this time with normal gastric juice or a potent concentrate of intrinsic factor from hog stomach, a large part

TABLE 1

Merits and Drawbacks of Isotope Methods for Measurement of Intestinal Absorption of Vitamin B_{12}, Presence or Absence of Intrinsic Factor in the Stomach, and Assay of Potency of Intrinsic Factor Preparations

Method	Merits	Drawbacks
1. Fecal excretion test (Heinle et al., 1952)[6]	1. Directly measures $Co^{60}B_{12}$ nonabsorbed in intestine, which by inference quantitates intestinal absorption of B_{12}. 2. Does not change the metabolic and clinical status of the patient.	1. Unrecognized loss of stool specimen might give false normal values.[12] 2. Normal and abnormal ranges of values are close to each other and may occasionally overlap.[23] 3. Seven to 10 days of stool collection are required. 4. Need for metabolic ward or utmost collaboration of patient and nursing personnel.[11] 5. Time consuming, laborious,[11,12] and esthetically unappealing.[11]
2. Urinary excretion flushing test (Schilling, 1953).[7]	1. Rapid (24–72 hours, depending upon modification used).[7,18,20] 2. Relative ease of processing and counting urines. 3. Rather clear-cut and not overlapping results.[16–22] 4. Flushing injection rids the body of about $\frac{1}{3}$ of absorbed radioactivity.[19,24] 5. Test may be repeated twice per week on the same patient, which makes it suitable for rapid assay of intrinsic factor preparations.[18,22]	1. Unrecognized loss of urinary specimen, especially in the first 8–12 hours, might falsify conclusions and suggest pernicious anemia in a normal person.[11,12] 2. Coexistent impairment of renal function prolongs renal clearance of radioactivity and falsifies results.[12,25] 3. No agreement between various investigators as to the dose, time of injection, and urine counting.[18] 4. Injection of large dose of nonradioactive B_{12} initiates maximal hematopoietic response in B_{12} deficiency anemias, changes their metabolic and clinical status, and precludes further laboratory studies.[11] 5. The method gives only relatively comparable data on B_{12} absorption but is unable to quantitate the intestinal absorption of vitamin B_{12}.[26] 6. Massive injection of B_{12} in some instances decreases intestinal B_{12} absorption[19,26] and the hepatic uptake of radioactivity[28] which precludes use of this method together with fecal excretion or hepatic uptake measurement simultaneously on the same patient.

TABLE 1—(*Continued*)

Method	Merits	Drawbacks
3. Serum radioactivity test (Doscherholmen and Hagen, 1956;[9] Booth and Mollin, 1956.[10])	1. Most rapid (8–12 hours). 2. Gives information on the efficiency of intestinal absorption of vitamin B_{12}. 3. Does not change the metabolic and clinical status of the patient.	1. Very low counts in serum when $Co^{60}B_{12}$ is used, which makes counting technics rather delicate. 2. Easy counts with large doses of $Co^{60}B_{12}$, but all usual drawbacks of handling radioactive material of short half-life time. 3. Coexisting impairment of renal function raises serum levels.[25] 4. Method gives only relative and comparable data on B_{12} absorption but does not quantitate them.
4. Hepatic uptake test. (a) original technic, (Glass et al., 1954).[8]	1. Does not require any specimen collections, which makes it independent of patient's cooperation.[11, 12] 2. Avoids errors due to loss of urine or stool specimen.[11, 12] 3. Hepatic radioactivity is directly proportional to amount of B_{12} absorbed.[10] 4. Measurements are simple and rapidly performed with routine equipment of clinical isotope laboratory.[10–12, 30–35] 5. No overlapping of normal and abnormal results.[11, 12, 29, 30] 6. Does not change the metabolic and clinical status of the patient. 7. May be performed with fecal excretion test simultaneously in same patient.[10, 11] 8. When followed by measurement of hepatic uptake after parenteral administration of the same dose of radioactive B_{12} the method allows quantitation of intestinal absorption of B_{12}.[29, 36]	1. Requires 1 wk. before results are obtained. 2. When used for repeated assays of potency of intrinsic factor preparations, a new base line of hepatic counts must be established by taking counts on two or three consecutive days and averaging them. 3. Some difficulties may arise in duplicating the liver projections on a patient on whom tests are repeated for several weeks. 4. Coexistent liver disease may or may not slightly decrease the hepatic uptake.[40]
(b) Accelerated method (48-hour test) (Glass, 1956).[41]	1, 2, 4, 5 and 6, as above 9. Requires only 48 hours for a single test, rarely 72 hours, which makes it suitable for routine diagnostic use. 10. When the uptake is nil or in traces, the test may be repeated immediately with addition of intrinsic factor preparation.	2, 3, and 4, as above 5. When used for the assay of potency of intrinsic factor preparations, the readings are taken on the 2nd or 3rd day, but in case of a positive uptake the next test cannot be repeated before 1 week.

of the radioactive B_{12} becomes absorbed in the intestine, as shown by the appearance of radioactivity over the liver.[8] This pattern is almost pathognomonic of pernicious anemia, and it is imitated only by patients after total gastrectomy, for obvious reasons.[37]

When we applied the hepatic uptake test to our patients with sprue, we found that most of them could not absorb vitamin B_{12} from the intestine and consequently could not deposit it in the liver. However, in contrast to pernicious anemia, this defective absorption defect could not be corrected by the addition of intrinsic factor preparation,[8, 38] since it was dependent upon a generalized defect in the absorptive capacity of the small intestine. Later, other authors using other methods observed similar absorption defects in sprue.[16-18] However, in some of the cases of idiopathic steatorrhea, a normal or only slightly impaired absorption of B_{12} in the intestine was found,[16-18, 39] and in others the existing defect in absorption could be partly overcome by the use of massive doses of preparations of intrinsic factor which were far in excess of physiologic amounts.[39]

The measurement of the hepatic radioactivity emanating from the Co^{60} B_{12} absorbed in the intestine and deposited in the liver can be performed only after the unabsorbed radioactive material has been eliminated from the intestine in stool. With the original method the hepatic counts can be taken only after a period of five to seven days has elapsed after administration of the tracer dose of radioactive B_{12}.[8, 10-12]

To expedite this procedure we have recently accelerated the removal of the unabsorbed $Co^{60}B_{12}$ from the intestine by administration of a cathartic and enema.[41] This allows one to take the counts as early as 48 hours after the administration of the tracer dose of radioactive B_{12}, though they have not yet reached their peak values.

Accelerated Method of Measurement of Hepatic Uptake of Radioactive Vitamin B_{12}

A tracer dose of 0.5 μg $Co^{60}B_{12}$, containing 0.45 or 0.5 μc of Co^{60}, is given in water by mouth, preferably in the morning on an empty stomach. The patient may eat two or three hours thereafter, but no vitamins or laxatives of any kind are allowed during the day. At the twenty-fourth hour one ounce of castor oil or a similar amount of Epsom salt is given. The next morning a thorough, cleansing enema is administered, and shortly thereafter, exactly 48 hours after administration of the tracer dose, the counts are taken.

The scintillation counter is applied in direct contact with and perpendicularly to the skin, without collimator, to two projections of the liver (in the middle of the hepatic dullness, anteriorly, i.e., in the midclavicular line, fifth or sixth intercostal space, and in midlateral line, ninth intercostal space), to two abdominal areas, serving as control (midway between umbilicus and symphysis, and midway between umbilicus and left anterior iliac

spine), and to the posterior mid aspect of the left thigh, which serves as body background. The counts are taken for five minutes over each of the five areas, so that the total counting procedure takes less than 30 minutes. The hepatic and abdominal counts are averaged separately, the body background is deducted from the averaged figures, and the hepatic uptake is calculated in counts per minute per microcurie of Co^{60}. Corrections for the decay of $Co^{60}B_{12}$ are not necessary, in view of the short time interval needed for the test.

If hepatic uptake is demonstrated and the abdominal counts show good evacuation of nonabsorbed labeled material (averaged abdominal counts below 60% of the averaged hepatic counts after deduction of the background), the test is finished after 48 hours. If no hepatic uptake is obtained, a second similar tracer dose of $Co^{60}B_{12}$ is given orally, this time together with a potent preparation of intrinsic factor, free of B_{12}. The laxative and enema are administered again after the same intervals as before, and counts are taken exactly 48 hours after the administration of the second tracer dose. Hepatic, abdominal and background counts are calculated and evaluated as before.

Thus the time required for the single test is two days—four days if the test with intrinsic factor is to be added. In about 10% of the cases in our experience, the abdominal counts on the third day were above 60% of hepatic counts, indicative of some retention of radioactive material in the intestine. In this instance another dose of laxative was given at once, followed by an enema, and counts were repeated the next morning, i.e., 72 hours after administration of the tracer material.

To obtain an optimal ratio between the background and hepatic counts, it might be preferable to set the high voltage just below the plateau level of the tube, and to use rather low sensitivity, in the neighborhood of 200 mv. This gives background as low as 70 to 130 counts per minute (cpm) when an unshielded counter is used. Such setting requires a scaler with a preamplifier, precision adjustment dials of high voltage and sensitivity, with micrometric knobs, and preferably a high voltage stabilizer to avoid drifting of voltage. However, any routine isotope equipment, such as that used for the measurement of the uptake of radioactive iodine by the thyroid, may be used also, provided the collimator is removed from the tube, the shielded crystal is held in direct contact with the skin, and the high voltage is set at the beginning of the plateau of the photomultiplier tube.

The efficiency of this 48-hour test was determined in 27 individuals by comparing the hepatic and abdominal counts obtained with this technic with those measured four to five days later, i.e., on the sixth or seventh day after the administration of a tracer dose, at which time the hepatic uptake is known to reach a peak.[8] It appears from the data shown in figure 1, which will be reported in greater detail elsewhere,[42] that the values of hepatic uptake on the seventh or eighth day in 24 instances out of 27 were higher than after

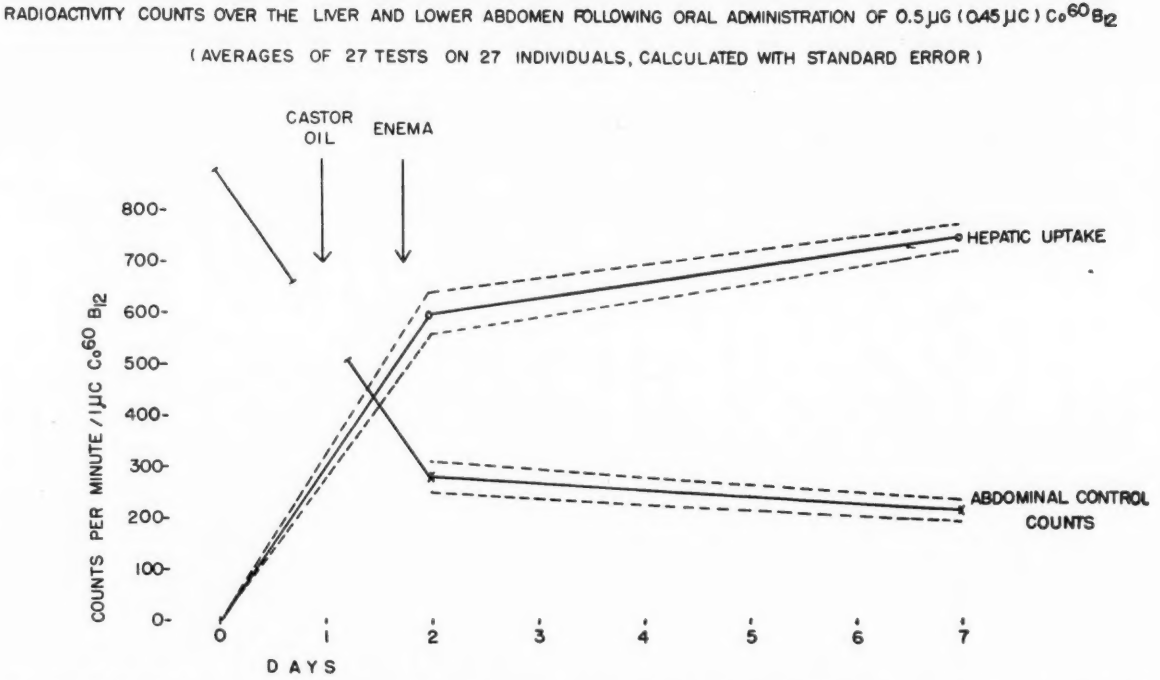

FIG. 1. Radioactivity counts over the liver and lower abdomen following oral administration of 0.5 µg (0.45 µc ($Co^{60}B_{12}$. Each curve represents the average of 27 tests on 27 individuals, calculated with standard error.

48 hours, on the average, by 25%. Thus, the 48-hour test strikes the ascending limb of the hepatic deposition before it reaches its peak, i.e., usually somewhere in its upper three quarters. However, the hepatic deposition at this time is already sufficient to be determined by external scintillation counting, so that the results obtained were entirely satisfactory for clinical purposes.

Case material includes 50 patients, 20 of whom had pernicious anemia; of these 20 patients, 10 were in relapse and 10 in complete hematologic remission; six had sprue (five with macrocytic anemia and one in the nonanemic stage); 12 had other nonpernicious macrocytic anemias, and 12 had anacidity refractory to histamine.

All of the patients with pernicious anemia in relapse were admitted with typical megaloblastic anemia, histamine-refractory anacidity, and more or less marked neurologic signs of posterior or combined degeneration of the cord. Later on, all were brought into complete hematologic and clinical remission by oral treatment with vitamin B_{12} and potent preparations of intrinsic factor. All patients with pernicious anemia in remission were proved cases of pernicious anemia who earlier had been admitted to our institution at the onset of the disease or in relapse, and who had since been kept on file and on maintenance treatment.

Of the 12 cases of nonpernicious macrocytic anemia, there were five of nutritional B_{12} or folic acid deficiency, two of macrocytic nonpernicious anemia of unknown origin, one of splenomegalic anemia of unknown origin, two of acquired hemolytic anemia, one of secondary macrocytic anemia associated with metastatic malignancy of the liver, and one of monocytic leukemia with macrocytic anemia.

The cases of anacidity refractory to histamine concerned individuals with various chronic ailments, such as diabetes (two cases), hypertensive cardiovascular disease (two cases), arteriosclerosis in old age (four cases), chronic gastritis (three cases, one of which was due to chronic alcoholism), and malnutrition (one case). In eight of these cases the anacidity was also confirmed with the urinary resin test.

Hepatic Uptake of $Co^{60}B_{12}$ in Pernicious Anemia in Relapse

In 10 patients with pernicious anemia and anacidity refractory to histamine (grouped in figure 1), the hepatic uptake of radioactivity following oral administration of $Co^{60}B_{12}$ alone either was nil or showed only traces. The addition of a potent preparation of intrinsic factor from animal sources in all instances corrected the defective absorption of B_{12} and raised the hepatic uptake of $Co^{60}B_{12}$ to normal or almost normal range (200 to 900 cpm/1 μc Co^{60}). The extent of the correction obtained depended partly upon the particular individual, but also upon the kind, potency and dose of the prepa-

ration of intrinsic factor used. (This was mostly equivalent to the dose contained in 1 to 2 USP units of oral antianemia preparation.)*

Figure 1 illustrates the uniformly defective pattern of B_{12} absorption in pernicious anemia. A case is given to exemplify the clinical significance of the measurement of the hepatic uptake for the diagnosis of pernicious anemia:

Case Reports

Case 1. A 44 year old Negro male was admitted because of fatigue of six months' duration, numbness in toes and fingers, and loss of appetite. Physical examination was essentially negative. Blood count: 2,800,000 red blood cells; 10.9 gm. (70%) hemoglobin; color index, 1.2; hematocrit, 33.0%; MCV, 117; MCH, 39. Reticulocytes, 0.7%. Bone marrow, erythroblastic. Gastric analysis: no free HCl in the fasting content, or after histamine. Neurologic examination: questionable decrease of vibratory sense in both feet; no other pathologic findings. Hepatic uptake: negative following oral administration of 0.5 μg $Co^{60}B_{12}$ alone, and highly positive after administration of a similar dose of $Co^{60}B_{12}$ together with a potent preparation of intrinsic factor. Oral administration of 15 μg vitamin B_{12} daily for 10 days did not result in a hematopoietic response, but an optimal clinical and hematopoietic response (reticulocytosis with a peak of 23% on the ninth day, a rise of red blood cells to 3,700,000, and hemoglobin to 12.5 gm. (80%) after two weeks of the treatment) was obtained on addition of potent concentrate of intrinsic factor to the same oral dose of B_{12}.

In this case the diagnosis of pernicious anemia was in doubt because of the questionable neurologic findings and nonmegaloblastic bone marrow. The measurement of the hepatic uptake aided in the diagnosis of pernicious anemia.

Hepatic Uptake in Nonpernicious Macrocytic Anemias

In the 12 cases of nonpernicious nutritional macrocytic anemia listed in figure 1, the hepatic uptake of $Co^{60}B_{12}$ was normal, that is, in the range found in controls, and did not significantly change after addition of intrinsic factor.

Positive hepatic uptake of $Co^{60}B_{12}$ permitted one to rule out pernicious anemia in many of these instances in spite of very strong evidence to the contrary. Many of the cases of macrocytic anemia had for years been erroneously considered and treated as pernicious anemia, but they have been properly relabeled with the aid of the hepatic uptake test.

Three illustrative cases are described below:

Case 2. A 65 year old female was admitted for weakness, inability to walk, complete anorexia and progressive general malaise of several months' duration. The patient drank excessively, and for the last several months had lived mainly on bread, starches, cooked vegetables and soups. She was overweight and very pale, with a slight yellowish tinge of the skin and sclerae. The tongue was normal but pale. There were no abnormalities in the viscera or the nervous system. Blood: red blood cells, 2,400,000; hemoglobin, 63%; color index, 1.3; reticulocytes, 1.5%; hematocrit,

* Generously supplied by Dr. K. W. Thompson, Medical Director and Vice-President of Organon, Inc., Orange, New Jersey.

28%; MCV, 114. Bone marrow, highly megaloblastic. A gastric analysis was refused by the patient. Hepatic uptake was normal following oral administration of radioactive B_{12} alone.

On the basis of hepatic uptake, lack of neurologic symptoms, and a history of alcoholism and dietary deficiency, nutritional macrocytic anemia was diagnosed. This was confirmed later by the rise in the blood count to 3,800,000 and reticulocytes to 14% following a normal hospital diet to which multiple vitamin capsules (containing B_{12} but not folic acid) had been added.

Case 3. A 38 year old Puerto Rican female had for months had progressive dizziness on walking and dyspnea on effort. Her appetite was good, and she had had no diarrhea. She had seven living children, the eldest 23, the youngest two. Nine years before she had been told she had anemia. There was a history of inadequate food intake, and she was underweight. There was pallor of the skin, but without a yellowish tinge. The liver and spleen were moderately enlarged. Blood count: red blood cells, 2,200,000; hemoglobin, 6.7 gm.; white blood cells, 2,700; color index, 1.0; reticulocytes, 0.1%; sedimentation rate, 45 mm./1 hr. Sugar tolerance curve, flat on both oral and intravenous administration, with peaks not exceeding 125 mg.%. All liver function tests were normal. Fragility of red cells, normal. Stool, negative for occult blood, parasites and fat on several examinations. A normal uptake of $Co^{60}B_{12}$ by the liver was found following oral administration of a tracer dose of $Co^{60}B_{12}$ alone.

The diagnosis of a nutritional macrocytic anemia with splenomegaly was made and its origin was related to the dietary deficiency and multiple pregnancies. An excellent clinical and hematologic improvement was obtained following treatment with a high caloric diet and folic acid.

Case 4. A 71 year old Puerto Rican female was admitted to the Metropolitan Hospital in 1951 complaining of weakness and loss of appetite. Because of general pallor, severe hyperchromic anemia, erythroblastic bone marrow and histamine-refractory anacidity, a diagnosis of pernicious anemia was made. The patient was treated with liver and placed on the Home Care Service. She was visited every two weeks for the next two years to receive injections of 2 c.c. liver extract and, more recently, 30 μg vitamin B_{12}. When seen in 1954 the patient was in complete remission, without any signs of disease, and her hepatic uptake was found to be normal.

The diagnosis of pernicious anemia for which the patient had been treated for two years was ruled out, and the diagnosis of malnutritional dietary deficiency was entertained. Supplemental history pointed to severe and prolonged malnutrition. The patient was placed on a high caloric, high protein and high vitamin diet, without folic acid but with B_{12} orally and for the last two years has been feeling fine without other treatment.

Hepatic Uptake of $Co^{60}B_{12}$ in Sprue

In four cases of sprue and a case of regional enteritis the characteristic defect of the intestinal absorption of vitamin B_{12} was found which was not corrected by addition of intrinsic factor. Of these five cases, three had been

erroneously labeled as pernicious anemia because of megaloblastic bone marrow, anacidity and severe macrocytic anemia. After measurement of the hepatic uptake showed a typical pattern for sprue the diagnosis was changed accordingly, and was later confirmed by the clinical course of the disease.

Two representative cases are here described more in detail:

Case 5. A 75 year old Puerto Rican male was admitted for progressive weakness, loss of appetite and exertional dyspnea of two to three years' duration. In 1951 a diagnosis of macrocytic nutritional anemia—possibly nontropical sprue—had been made. On his second admission (1952) the same diagnosis had been made. Each time the patient was treated parenterally with B_{12} and improved markedly. Gastroscopy performed on his second admission showed atrophic gastritis. No abnormality was found in the gastrointestinal tract on x-ray examination.

On the patient's third admission, in 1954, there was pallor of the skin, with a slight yellowish tint. The tongue was smooth and pale. No other abnormalities were found in the internal organs. The reflexes and kinesthetic sense were normal.

Blood count: red blood cells, 1,810,000; hemoglobin, 6.5 gm.; color index, 1.1; reticulocytes, 1.5; hematocrit, 22.0; MCV, 121; MCH, 36; MCHC, 29; white blood cells, 4,350, with 58% neutrophils, 38% lymphocytes and 4% monocytes. Gastric analysis showed no free acid after histamine. On examination of the stool, fat and fatty acids were reported as negative.

An x-ray examination of the gastrointestinal tract showed spasticity of the duodenal bulb but no abnormality of the mucosal pattern of the small intestine.

Glucose tolerance test: fasting, 88 mg.%; after one hour, peak value, 119 mg.%. Cephalin flocculation, negative. Serum bilirubin, 1.14 mg.%; icteric index, 12. Because of anacidity, a smooth tongue, increased bilirubin in the blood, severe megaloblastic anemia, lack of diarrhea, and good results obtained with parenteral treatment with vitamin B_{12}, doubts were voiced as to a diagnosis of sprue, and the possibility of pernicious anemia was seriously considered.

However, measurement of the hepatic uptake of $Co^{60}B_{12}$ revealed a block to intestinal absorption of B_{12} which was not overcome by the addition of intrinsic factor. This confirmed the initial diagnosis of sprue, and subsequently was further supported by a lack of hematopoietic response to oral administration of vitamin B_{12}, together with potent preparations of intrinsic factor. An hematopoietic response was obtained when this treatment was associated with daily intramuscular administration of ACTH, and there was an optimal hematopoietic response to intramuscular administration of vitamin B_{12}.

Case 6. A 67 year old Puerto Rican female was admitted complaining of pains in the right upper abdomen. A year before she had been operated on for gall-stones. Since then she had had occasional bouts of diarrhea, which had been diagnosed as biliary disturbances.

Physical examination revealed nothing remarkable. The blood count was normal. A gastric analysis showed the presence of gastric anacidity under fasting conditions and after histamine stimulation. Repeated tests of hepatic uptake showed no uptake of $Co^{60}B_{12}$ following oral administration of radioactive vitamin alone or together with intrinsic factor. A diagnosis of sprue in remission was made on the basis of the isotope test, and previous hospital records of the patient were requested. These showed that the patient had been hospitalized a few years before for persistent diarrhea and sore tongue. A gastrointestinal series at that time had shown fragmentation of barium throughout the lower small intestine, suggestive of disordered motor function. A flat blood sugar tolerance curve was also found, and the diagnosis of sprue

was made at that time. The patient was treated with folic acid and crude liver, which resulted in complete clinical recovery that has persisted to the present.

Thus, the hepatic uptake test can detect sprue in an asymptomatic stage.

Hepatic Uptake of $Co^{60}B_{12}$ in Pernicious Anemia in Remission

Ten cases of known pernicious anemia in remission were studied. The results obtained are listed in figure 2. All of these cases had at some previous date been admitted to our institution in full relapse or at the onset, and at that time had shown typical megaloblastic anemia, anacidity refractory to histamine, and neurologic signs of posterior or combined degeneration of the cord. All had been brought into complete remission by oral treatment with vitamin B_{12} and a potent preparation of intrinsic factor. In all these cases, while in remission, the hepatic uptake of $Co^{60}B_{12}$ was nil or found only in traces. In all, the addition of intrinsic factor has resulted in correction of the negative hepatic uptake of B_{12} and deposition of $Co^{60}B_{12}$ in the liver. The results of the isotope test were uniform, and were diagnostic for pernicious anemia. They were identical with those obtainable in cases of pernicious anemia in relapse.

Hepatic Uptake Measurements in Anacidity Refractory to Histamine

Of the 12 patients with gastric anacidity refractory to histamine listed in figure 2, in nine the range of hepatic uptake was normal following oral administration of $Co^{60}B_{12}$ alone or together with a potent intrinsic preparation. This is in contrast to the pattern presented by patients with pernicious anemia and gastric anacidity.

The difference in the results of the isotope test in both groups with anacidity obviously depends upon the amount of intrinsic factor secreted in the stomach and apparently allows one to distinguish between complete gastric atrophy of pernicious anemia and partial or patchy atrophy of the gastric mucosa in simple anacidity. The following case illustrates the significance of this measurement for clarification of the nature of some cases of gastric anacidity associated with neurologic signs.

Case 7. A 56 year old male, for many years a chronic alcoholic with occasional bouts of dipsomania lasting for several days, had for the last few weeks had loss of appetite, general weakness, numbness and tingling in the lower extremities, especially in the left foot, and fatigue.

Physical examination revealed no pathologic findings except for slight pallor of the skin and a somewhat smooth tongue, especially on its edges. Gastric analysis revealed complete anacidity, refractory to histamine. Stools were negative for occult blood. A gastrointestinal x-ray series and a barium enema were negative. Blood count: red blood cells, 3,750,000; hemoglobin, 80%; color index, 1.1; white blood cells, 4,600, with a normal differential.

Because of the patient's weakness, anacidity, loss of appetite and neurologic

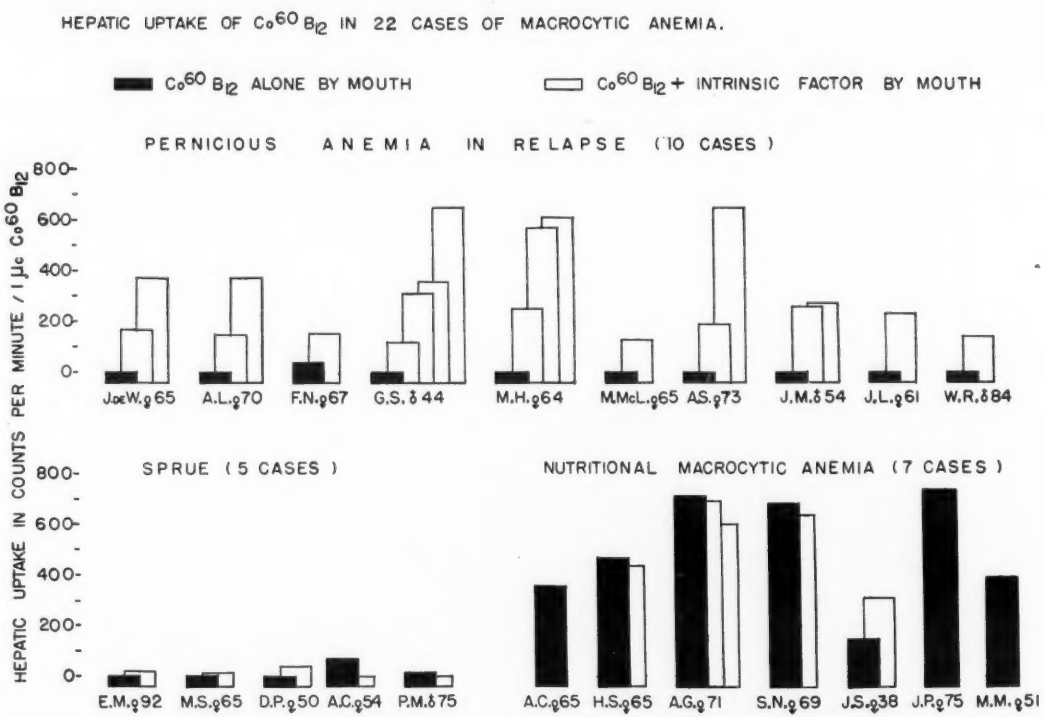

FIG. 2. Hepatic uptake of $Co^{60}B_{12}$ in 22 cases of macrocytic anemia.

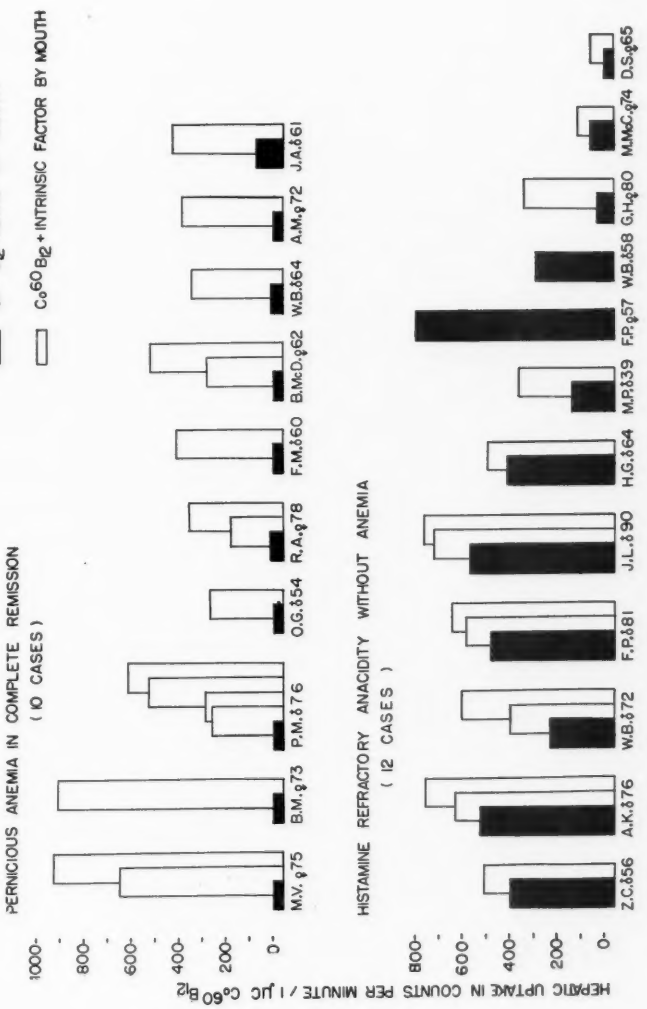

FIG. 3. Hepatic uptake of $Co^{60}B_{12}$ in 22 cases of anacidity with normal blood count.

symptoms, the diagnosis was entertained of pernicious anemia at the onset, with beginning degeneration of the cord. Measurements of hepatic uptake were normal and thus ruled out this diagnosis. Subsequently, x-ray examination of the lumbar spine revealed herniation of the disc (L_5–S_1) as the cause of the neurologic symptoms.

In three of our 12 cases of anacidity refractory to histamine, hepatic measurements of hepatic uptake have shown a block to intestinal absorption of vitamin B_{12}. In one of these cases the addition of intrinsic factor preparation has markedly increased the hepatic uptake of $Co^{60}B_{12}$; in two others this improvement was less marked, and the pattern more nearly resembled that observed in sprue. These three patients belonged to the older age group, were essentially asymptomatic, and showed a normal blood count. It is impossible to say at this time whether they represented instances of unrecognized pernicious anemia, or sprue in complete remission, due to some previous treatment (no indication to this effect was found in their history), or whether they should be considered as possible precursors of these diseases. More observations of this kind in the future may lead to the detection of precursors of pernicious anemia or asymptomatic sprue among the general population.

Conclusions

The measurement of hepatic uptake of $Co^{60}B_{12}$ aids in (1) the differentiation of various macrocytic anemias; (2) the detection or ruling out of pernicious anemias, both in relapse and in remission; (3) the diagnosis of sprue especially in the oligosymptomatic or asymptomatic stage of disease, and (4) the differentiation of simple anacidity refractory to histamine from that due to the gastric atrophy of pernicious anemia in non-anemic or preanemic stage.

The hepatic uptake is normal in anemias due to blood loss, hemolytic anemias, and nutritional macrocytic anemias due to dietary deficiency of folic acid or B_{12}. On the contrary, the hepatic uptake is either entirely abolished or found only in traces in patients with pernicious anemia, in relapse, remission, or in the preanemic stage, but it can then be corrected by the addition of intrinsic factor. In sprue, and in some cases of regional enteritis or intestinal shunt, the hepatic uptake is also zero or appears only in traces, but it cannot be corrected by the addition of intrinsic factor.

Measurement of the hepatic uptake in its accelerated form allows one to rule out pernicious anemia in 48 hours, and to make a diagnosis of pernicious anemia or sprue within four days, without regard to the previous treatment or to the stage of the disease. In time requirement it matches the urinary flushing test and is not subject to errors due to the inadvertent discarding of a urinary specimen by the patient. The test can be performed in any clinical isotope laboratory which has the ordinary equipment for the measurement of the uptake of radioactive iodine by the thyroid, and the actual single measurement takes only 30 minutes.

Summario in Interlingua

Le mesuration del acceptation hepatic de vitamina B_{12} a Co^{60} ha essite simplificate e accelerate pro render lo utile in le differentiation clinic del anemias macrocytic e le detection de formas asymptomatic de anemia perniciose e sprue. Un dose traciator de 0,5 μg de B_{12} a Co^{60}—continente 0,35 a 0,50 μc de Co^{60}—es administrate per via oral ante le prime repasto del die. Vinti-quatro horas plus tarde, un uncia de oleo de ricino es administrate; le matino sequente, un clyster. Postea, exactemente 48 horas post le administration del B_{12} a Co^{60}, contos al exterior del corpore es effectuate per medio de un contator de scintillation in contacto directe con le pelle sin collimator e durante cinque minutas in cata un de cinque areas del corpore: (1 e 2) Le projectiones medie-lateral e anterior del hepate in le lineas medie-axillar e medie-clavicular (contos hepatic); (3 e 4) le abdomine sinistro-inferior e medie-inferior (contos abdominal); e (5) musculo sural del gamba sinistre (radiation de fundo del corpore). Le acceptation hepatic es calculate per minuta e per 1 μc de Co^{60} post le deduction del radiation de fundo del corpore ab le valor medie del contos hepatic. Le conto abdominal provide valores de controlo pro le evacuation de non-absorbite material radioactive ab le intestino. Si illo es plus que 60% del conto hepatic, un secunde cathartico es administrate, e le conto es repetite le sequente die.

Si un positive acceptation hepatic de radioactivitate es constatate, le anemia es le effecto de perdita de sanguine, augmento de hemolyse, carentia de ferro, o carentia dietari de B_{12} o acido folic, e le possibilitate de anemia perniciose es eliminate. Si nulle acceptation hepatic de B_{12} a Co^{60} es constatate (o solmente tracias de un tal), le integre processo es repetite post le administration de un nove dose de B_{12} a Co^{60} oral, iste vici insimul con potente factor intrinsec (i.e. le commercialmente obtenibile concentrato de factor intrinsec con un potentia de 2 unitates anti-anemic (del Statotunitese Pharmacopeia), sin ulle contento de vitamina B_{12}, o 75 a 100 ml de filtrate succo gastric ab un normal subjecto human).

Nulle acceptation hepatic de radioactivitate post le administration de B_{12} a Co^{60} insimul con material continente factor intrinsec indica sprue o syndrome de malabsorption como effecto de un altere morbo del intestino tenue. Un positive acceptation hepatic de B_{12} a Co^{60} sub iste conditiones—vole dicer: nulle acceptation quando B_{12} a Co^{60} oral es administrate sin factor intrinsec—es typic in casos de anemia perniciose in recidiva, remission, o stadio preanemic e post gastrectomia total.

Plus que 30 non-recognoscite, misdiagnosticate, o dubitose casos de asymptomatic sprue, anemia perniciose in remission complete post tractamento, e varie anemias macrocytic esseva correctemente reidentificate e diagnosticate per iste methodo.

Le mesuration del acceptation hepatic de B_{12} a Co^{60} es estiam utile in differentiar simple anaciditate histamino-resistente ab anaciditate causate per atrophia gastric in anemia perniciose.

Le test pote esser effectuate in omne laboratorio clinic pro studios isotopic que possede le normal apparaturas pro le mesuration del acceptation de iodo radioactive per le glandula thyroide. Le mesuration mesme require solmente 30 minutas. Le tempore total del test es simile a illo del test a elution de urina, sed illo non suffre del possibilitate de errores causate per le inadvertente disjection de specimens de urina per le patiente.

BIBLIOGRAPHY

1. Castle, W. B.: Observations on etiologic relationship of achylia gastrica to pernicious anemia. 1. Effect of administration to patients with pernicious anemia of contents of normal human stomach recovered after ingestion of beef muscle, Am. J. M. Sc. **178**: 748, 1929.
2. Doig, R. K., and Wood, L. J.: Gastric biopsy in pernicious anemia, M. J. Australia **2**: 565 (Oct. 14) 1950.

3. Minot, G. R., and Castle, W. B.: Interpretation of reticulocyte reactions: their value in determining the potency of therapeutic materials, especially in pernicious anemia, Lancet **2**: 319, 1935.
4. Chaiet, L., Rosenblum, C., and Woodbury, D. T.: Biosynthesis of radioactive vitamin B_{12} containing Co^{60}, Science **111**: 601, 1950.
5. Bradley, J. E., Smith, L. E., Baker, S. J., and Mollin, D. L.: The use of the radioactive isotope of cobalt Co^{58} for the preparation of labelled vitamin B_{12}, Lancet **2**: 476 (Sept. 4) 1954.
6. Heinle, R. W., Welch, A. D., Scharf, V., Meacham, G. C., and Prusoff, W. H.: Studies of excretion (and absorption) of Co^{60}-labeled vitamin B_{12} in pernicious anemia, Tr. A. Am. Physicians **65**: 214, 1952.
7. Schilling, R. F.: Intrinsic factor studies. II. The effect of gastric juice on the urinary excretion of radioactivity after the oral administration of radioactive vitamin B_{12}, J. Lab. and Clin. Med. **42**: 860, 1953.
8. Glass, G. B. J., Boyd, L. J., Gellin, G. A., and Stephanson, L.: Uptake of radioactive vitamin B_{12} by the liver in humans; test for measurement of intestinal absorption of vitamin B_{12} and intrinsic factor activity, Arch. Biochem. and Biophys. **51**: 251, 1954.
9. Doscherholmen, A., and Hagen, P. S.: Radioactive vitamin B_{12} absorption studies: results of direct measurement of radioactivity in the blood, J. Clin. Investigation **35**: 699, 1956.
10. Booth, C. C., and Mollin, D. L.: Plasma, tissue, and urinary radioactivity after oral administration of ^{56}Co-labelled vitamin B_{12}, Brit. J. Hematol. **2**: 223, 1956.
11. Pollycove, M., and Apt, L.: Absorption, elimination and excretion of orally administered vitamin B_{12} in normal subjects and in patients with pernicious anemia, New England J. Med. **255**: 207, 1956.
12. (a) Bull, F. E., Campbell, D. C., and Owen, C. A., Jr.: The diagnosis and treatment of pernicious anemia, M. Clin. North America **40**: 1005, 1956.
    (b) Bull, F. E., Campbell, D. C., and Owen, C. A., Jr.: Evaluation of intrinsic factor in pernicious anemia by means of cobalt^{60} vitamin B_{12}, Abstract, Federation Proc. **15**: 509, 1956.
13. Halsted, J. A., Swendseid, M. E., Lewis, P. M., and Gasster, M.: Mechanisms involved in the development of vitamin B_{12} deficiency, Gastroenterology **30**: 21, 1956.
14. Halsted, J. A., Lewis, P. M., Hvolboll, E. E., Gasster, M., and Swendseid, M. E.: An evaluation of the fecal recovery method for determining intestinal absorption of cobalt^{60}-labeled vitamin B_{12}, J. Lab. and Clin. Med. **48**: 92, 1956.
15. Callender, S., Turnbull, A., and Wakisaka, G.: Estimation of intrinsic factor of Castle by use of radioactive vitamin B_{12}, Brit. M. J. **2**: 10, 1954.
16. Krevans, J. R., Conley, C. L., and Sachs, M. V.: Radioactive tracer tests for the recognition and identification of vitamin B_{12} deficiency states, J. Chron. Dis. **3**: 234, 1956.
17. Reisner, E. H., Jr., Gilbert, J. P., Rosenblum, C., and Morgan, M. C.: Applications of the urinary tracer test (of Schilling) as an index of vitamin B_{12} absorption, Am. J. Clin. Nutrition **4**: 134, 1956.
18. (a) Best, W. R., White, W. F., Robbins, K. C., Landmann, W. A., and Steelman, S. L.: Studies on urinary excretion of vitamin $B_{12}Co^{60}$ in pernicious anemia for determining effective dosage of intrinsic factor concentrates, Blood **11**: 338, 1956.
    (b) Best, W. R., Landmann, W. A., and Limarzi, L. R.: Time pattern of vitamin $B_{12}Co^{60}$ urinary excretion in man after oral administration and parenteral "flushing," Blood **11**: 352, 1956.
19. Callender, S. T., and Evans, J. R.: The urinary excretion of labelled vitamin B_{12}, Clin. Sc. **14**: 295, 1955.
20. (a) Ellenbogen, L., Williams, W. L., Rabiner, S. F., and Lichtman, H. C.: An improved urinary excretion test as an assay for intrinsic factor, Proc. Soc. Exper. Biol. and Med. **89**: 357, 1955.

(b) Ellenbogen, L., and Williams, W. L.: Improved urinary excretion test for assay of intrinsic factor. II. Sensitive counting technic, Proc. Soc. Exper. Biol. and Med. **91**: 617, 1956.

21. Klayman, M. I., and Brandborg, L.: Clinical application of cobalt^{60}-labeled vitamin B_{12} urine test, New England J. Med. **253**: 808, 1955.
22. Tabern, D. L., Schwartz, S., Maslow, W., Talso, P., Storey, R., Lahr, T. N., and Osterberg, A. E.: Some new developments in the diagnostic use of radioisotopes, Second Clinical Meeting of the Society for Nuclear Medicine, Portland, Oregon, 1955.
23. Doscherholmen, A., and Hagen, P. S.: Clinical evaluation of the Schilling test, 6th Congress, International Society of Hematology, Boston, Abstr. No. 238, p. 249, 1956.
24. MacLean, L. D.: The differentiation of achylia gastrica and achlorhydria by means of radioactive vitamin B_{12}, Gastroenterology **29**: 653, 1955.
25. Rath, C. E., McCurdy, P. R., Duffy, B. J., and Howley, J. R.: Value and limitations of cobalt$^{60}B_{12}$ test, Blood **11**: 96, 1956.
26. Mollin, D. L., and Baker, S. J.: The absorption and excretion of vitamin B_{12} in man, Proceedings of the Biochemistry Society, London, 337th Meeting, February 19, 1955, p. 28.
27. Baker, S. J., and Mollin, D. L.: The relationship between intrinsic factor and the intestinal absorption of vitamin B_{12}, Brit. J. Hematol. **1**: 46, 1955.
28. Glass, G. B. J., Stephanson, L., Rosen, S., and Laughton, R.: Hepatic uptake and urinary excretion of radioactive B_{12} in assay of intrinsic factor, Federation Proc. **14**: 184, 1955.
29. Arias, I. M., Apt, L., and Pollycove, M.: Absorption of radioactive vitamin B_{12} in nonanemic patients with combined-system disease, New England J. Med. **255**: 164, 1956.
30. Pollycove, M., Apt, L., and Colbert, M.: Pernicious anemia due to dietary deficiency of vitamin B_{12}, New England J. Med. **255**: 164, 1956.
31. Meyer, L. M., Berlin, N. I., Jiminez-Casado, M., and Arkun, S. N.: Vitamin B_{12} distribution, determined by surface body counting following parenteral administration of Co^{60} vitamin B_{12}, Proc. Soc. Exper. Biol. and Med. **91**: 129, 1956.
32. Meyer, L. M., Arkun, S. N., and Jiminez-Casado, M.: Further observations on distribution of radioactivity following parenteral administration of Co^{60} vitamin B_{12}, Proc. Soc. Exper. Biol. and Med. **92**: 515, 1956.
33. Miller, A., Corbus, H. F., and Sullivan, J. F.: The plasma disappearance, excretion and tissue distribution of intravenous cobalt^{60} vitamin B_{12} in normal subjects and patients with chronic myelogenous leukemia, J. Clin. Investigation **35**: 724, 1956.
34. Schloesser, L. L., and Schilling, R. F.: Biologic half-life of hepatic radioactivity from vitamin $B_{12}Co^{60}$, 6th Congress, International Society of Hematology, Boston, Abstr. No. 235, p. 245, 1956.
35. Estren, S., and Oxenhorn, S.: The plasma transport, tissue storage, and urinary excretion of radioactive vitamin B_{12}, 6th Congress, International Society of Hematology, Boston, Abstr. No. 236, p. 246, 1956.
36. (a) Glass, G. B. J., Boyd, L. J., and Stephanson, L.: Inverse relationship between intake and utilization of vitamin B_{12} in the intestine, Federation Proc. **13**: 54, 1954.
    (b) Glass, G. B. J., Boyd, L. J., and Stephanson, L.: Intestinal absorption of vitamin B_{12} in man, Science **120**: 74, 1954.
    (c) Glass, G. B. J., Boyd, L. J., and Stephanson, L.: Intestinal absorption of vitamin B_{12} in humans as studied by isotope technic, Proc. Soc. Exper. Biol. and Med. **86**: 522, 1954.
37. Glass, G. B. J., Pack, G. T., and Mersheimer, W. L.: Uptake of radioactive vitamin B_{12} by the liver in patients with subtotal and total gastrectomy, Gastroenterology **29**: 666, 1955.
38. Glass, G. B. J.: Intestinal absorption and hepatic uptake of vitamin B_{12} in diseases of the gastrointestinal tract, Gastroenterology **30**: 37, 1956.

39. Callender, S. T., and Evans, J. R.: Observations on the relationship of intrinsic factor to the absorption of labelled vitamin B_{12} from the intestine, Clin. Sc. **14**: 387, 1955.
40. Glass, G. B. J., Ebin, L. M., Boyd, L. J., and Laughton, R.: Hepatic uptake of radioactive vitamin B_{12} in liver disease, Federation Proc. **15**: 235, 1956.
41. Glass, G. B. J.: Differentiation of macrocytic anemias and detection of pernicious anemia and sprue in remission by accelerated measurement of hepatic uptake of radioactive $Co^{60}B_{12}$, 6th Congress, International Society of Hematology, Boston, Abstr. No. 240, p. 251, 1956.
42. Glass, G. B. J., and Shaffer, H.: Further studies on the intestinal absorption of vitamin B_{12}, Bull. N. Y. Med. Coll., Flower and Fifth Ave. Hosps., in press.

STUDIES OF B_{12} Co^{60} ABSORPTION IN MALABSORPTION SYNDROME: RESULTS BEFORE AND DURING SPECIFIC THERAPY *

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MALABSORPTION syndrome can be defined as a disorder resulting from a defect in the intestinal absorption of various substances, including protein, fat, vitamins and minerals. The syndrome is a manifestation of various gastrointestinal disorders, such as sprue, regional enteritis, intestinal strictures and anastomoses, hypogammaglobulinemia and pancreatic dysfunction. In patients with this disorder, variability in the extent of the absorptive defect is often encountered. Relapses and remissions are common.

Since there are multiple absorptive defects in the syndrome, numerous tests have been utilized to measure defects in the absorption of fat, protein, carbohydrate and vitamins. The relative simplicity of the technics for determining absorption of radioactive vitamin B_{12} offers an ideal method for assaying this particular defect. Citing technics employing fecal excretion,[1] hepatic deposition [2] and urinary excretion,[3] reports in the literature would indicate that patients with sprue, severe regional enteritis and blind loop syndrome show impairment of vitamin B_{12} absorption that is not correctable by the oral administration of a potent intrinsic factor.[4, 5, 6, 7, 8] However, Turnbull [9] reported three examples of normal B_{12} absorption in steatorrhea.

We embarked on this study to test the validity of the Schilling test as a means of diagnosing the malabsorption syndrome and evaluating the procedure as an objective criterion of effective therapy. All cases of malabsorption selected for study were reviewed and confirmed by gastroenterologists on the staff of the Hospital of the University of Pennsylvania.

METHODS

A modified Schilling test was used, employing 0.2 to 0.3 μg of vitamin B_{12} Co^{60} with an activity of approximately 1.0 μc per microgram. A "flushing" dose of 1 mg. vitamin B_{12} was given intramuscularly simultaneously

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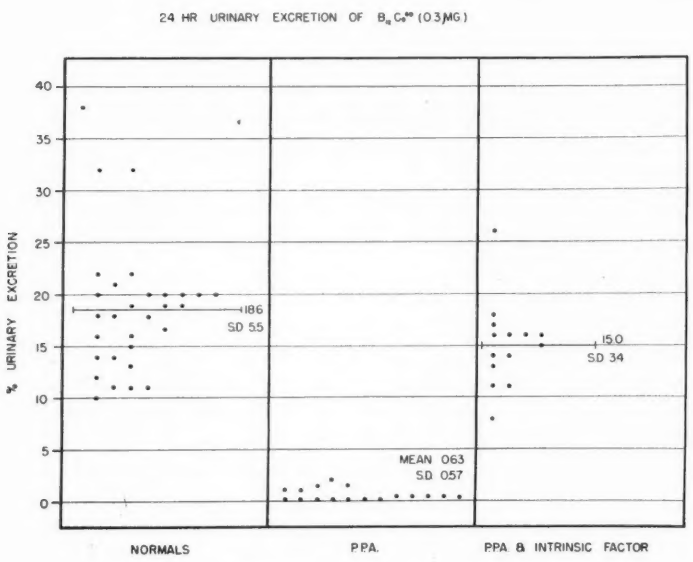

FIG. 1.

with the oral dose of radioactive B_{12}. Two hundred fifty cubic centimeter aliquots of 24-hour urines were concentrated and counted in duplicate in a well-type scintillation counter.

Patients suitable for specific therapy were studied before therapy and restudied after treatment was under way. Whenever possible, patients who were being treated when this study was started were taken off all drugs in order to obtain values under control conditions. Dosages of prednisone,* 12.5 to 20 mg. per day, or its equivalent in cortisone, were used over periods of from two weeks to several months. Tetracycline was given at doses of 1 gm. per day, and full dosages of potent intrinsic factor were employed. Repetition of the test in the same patient under similar conditions in five instances showed close agreement, thus establishing to our satisfaction that the test is quantitatively valid.

RESULTS

Figure 1 shows the results in normal patients and in patients with pernicious anemia, with and without simultaneous administration of intrinsic factor. Mean 24-hour urinary excretion in 30 normal patients was 18.6%, with a standard deviation of 5.5. Patients with pernicious anemia showed a mean urinary excretion of 0.63%, with a standard deviation of 0.57, which after simultaneous administration of intrinsic factor rose to a mean of 15%, with a standard deviation 3.4.

* Supplied by Dr. George Babcock, Schering Corp.

Results in five patients with sprue are illustrated in figure 2. Three patients showed impaired absorption, while two were in the normal range. Of two patients who received prednisone, one showed a significant increase in absorption of vitamin B_{12} whereas the other showed a decrease. One patient (J. R.), who was treated with a gluten-free diet, showed marked improvement radiologically and clinically in spite of a decrease in B_{12} absorption when tested after four and eight weeks of treatment.

Patient G. C. showed marked clinical improvement immediately following institution of prednisone therapy. Patient G. P. had been carefully followed in the Gastrointestinal Clinic of the Hospital of the University of Pennsylvania for 10 years. During this time he had had many episodes of steatorrhea and several attacks of tetany. He had been unresponsive to therapy with steroids, and diet, but had never received antibiotics prior to our study. Repeated gastrointestinal x-rays had shown only altered motor function, with no evidence of fistula, blind loop or stricture. He had shown impaired vitamin B_{12} absorption without specific therapy, while on steroids, and with simultaneous administration of intrinsic factor. After the administration of only 1.75 gm. of tetracycline his vitamin B_{12} absorption increased to the normal range and remained normal when repeated four weeks after cessation of the antibiotic. We do not know whether this effect can be attributed to the small amount of tetracycline, or whether it illustrates the

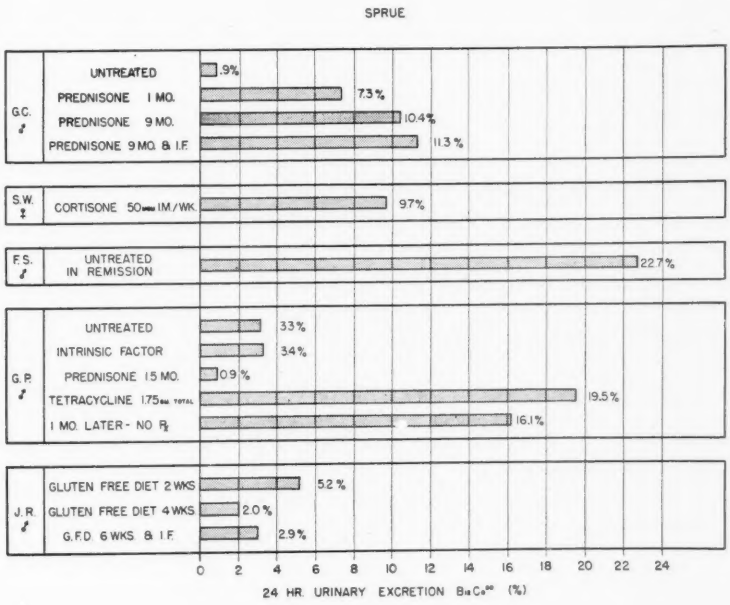

FIG. 2.

variability of absorption in this disease. In spite of increased absorption of vitamin B_{12} following antibiotic administration, this patient still had symptoms when the study was performed. The two patients (S. W. and F. S.) who showed normal vitamin B_{12} absorption were asymptomatic at the time of study. One (S. W.) was on small doses of cortisone (50 mg. per week intramuscularly).

In figure 3 results of our studies on patients with agammaglobulinemia and blind loop syndrome are illustrated. Both patients with agammaglobulinemia had steatorrhea similar to that which has been reported in this disease. One patient (P. M.) had normal vitamin B_{12} absorption before and during steroid therapy, although steatorrhea disappeared while on therapy. In contrast, patient M. J. had markedly decreased vitamin B_{12} absorption on four separate studies done before and during steroid therapy for periods of from one week to four months. During this time she nevertheless showed marked clinical improvement.

The two patients with blind loop syndrome showed consistently low absorption of vitamin B_{12}. In patient A. R. there was no increase while on therapy with cortisone, intrinsic factor or tetracycline for six days. This is in contrast to results reported by Halsted et al.,[10] who showed a significant increase after only three days of Aureomycin or tetracycline therapy.

Figure 4 represents our observations in patients with regional enteritis, subtotal gastrectomy, cystic fibrosis of the pancreas, and extensive small intestinal resection. Four patients with symptomatic regional enteritis and one patient with subtotal gastrectomy showed normal B_{12} absorption. A second patient (J. S.) with subtotal gastric resection showed low absorption. Unfortunately, we were unable to repeat this study utilizing a preparation of intrinsic factor. A very low absorption was found in patient F. S. when

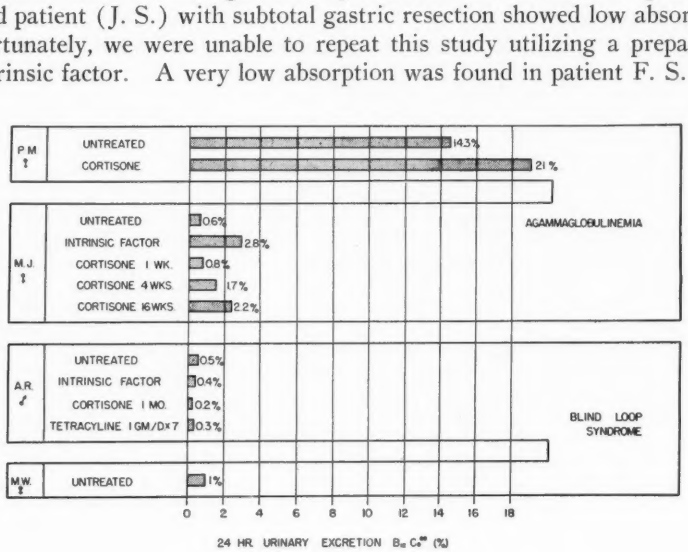

FIG. 3.

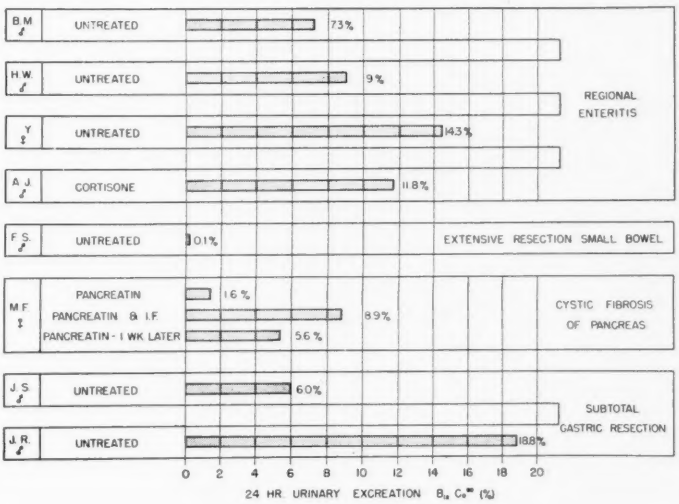

FIG. 4.

studied after resection of all but one foot of his small intestine because of superior mesenteric arterial thrombosis. Patient M. F., who has cystic fibrosis of the pancreas, had been extensively studied at the Hospital of the University of Pennsylvania over a three-year period. She shows all the classic manifestations of the disease, including fibrocystic disease of the lung, steatorrhea, cachexia, absence of exocrine pancreatic secretion, increased sodium and chloride in sweat, and laboratory findings consistent with cirrhosis. Anemia has never been observed during the entire period of observation. She had been on oral pancreatic extract (pancreatin) for a number of years. The first study showed low absorption of vitamin B_{12}; when tested one week later with intrinsic factor, absorption was increased to the lower limit of normal, but when tested one week later the absorption was again low. It is possible that the multiple glandular defects known to be present in cystic fibrosis of the pancreas may involve the gastric secretory cells responsible for production of intrinsic factor. This hypothesis is under study at the present time.

SUMMARY

1. The vitamin B_{12} absorption test is not a diagnostic test of the malabsorption syndrome.

2. In patients who had decreased absorption of vitamin B_{12} prior to specific therapy, clinical improvement was not consistently accompanied by increased absorption while on therapy. Furthermore, one patient who

showed increased absorption of vitamin B_{12} after tetracycline did not show clinical improvement.

3. Patients with agammaglobulinemia and cystic fibrosis of the pancreas may have low vitamin B_{12} absorption.

Summario in Interlingua

Patientes con syndrome de malabsorption (sprue, enteritis regional, stricturas e anastomoses intestinal, fibrosis pancreatic, e agammaglobulinemia) esseva studiate —ante e durante le therapia—con respecto a lor capacitate de absorber vitamina B_{12}. Le methodo usate esseva un modification del test de Schilling. Individuos normal monstrava un excretion medie de 18,6 pro cento in le urina de 24 horas. Le excretion medie in patientes con primari anemia perniciose esseva 0,63 pro cento. Iste valor se augmentava a 15,0 pro cento con administrationes potente de factor intrinsec. Inter cinque patientes con sprue, duo habeva un absorption normal de vitamina B_{12}. In tres le absorption esseva basse. In un del patientes de sprue con basse absorption, le administration de steroides esseva accompaniate per un augmento del absorption de vitamina; in un altere le absorption de vitamina remaneva inalterate sed cresceva a nivellos normal post le administration de 1,75 g de tetracyclina. Inter duo patientes con syndrome de malabsorption secundari a agammaglobulinemia, le un monstrava un absorption normal, le altere un absorption basse. Ambe iste patientes se meliorava clinicamente con administrationes de steroides, sed in ambes le absorption de vitamina B_{12} remaneva inalterate. Omne le patientes con symptomatic enteritis regional habeva un absorption normal de vitamina B_{12}. Un patiente con strictura intestinal habeva un basse absorption que non esseva alterate per un therapia con steroides e antibioticos.

Un patiente con fibrosis cystic del pancreas monstrava un basse absorption de vitamina B_{12}. Isto esseva augmentate a nivellos normal per le administration de factor intrinsec.

Super le base de iste studios nos ha concludite: (1) Le test del absorption de vitamina B_{12} non es diagnostic pro le syndrome de malabsorption; (2) in patientes qui habeva reducite nivellos del absorption de vitamina B_{12} ante le institution de therapias specific, le melioration clinic non esseva regularmente accompaniate de augmentos del absorption durante le application del therapia; e (3) patientes con agammaglobulinemia e fibrosis cystic del pancreas pote haber basse nivellos del absorption de vitamina B_{12}.

BIBLIOGRAPHY

1. Heinle, R. W., Welch, A. D., Scharf, V., Meacham, G. C., and Prusoff, W. H.: Studies of excretion (and absorption) of Co^{60} labelled vitamin B_{12} in pernicious anemia, Tr. A. Am. Physicians **65**: 214, 1952.
2. Glass, G. B. J., Boyd, L. J., Gellin, G. A., and Stephanson, L.: Uptake of radioactive vitamin B_{12} by the liver in humans: tests for measurement of intestinal absorption of vitamin B_{12} and intrinsic factor activity, Arch. Biochem. **51**: 251, 1954.
3. Schilling, R. F.: A new test for intrinsic factor activity, J. Lab. and Clin. Med. **42**: 946, 1953.
4. Best, W. V., White, W. F., Louis, J., and Lemarzi, L. R.: Experiences with the Schilling test using Co^{60} labelled vitamin B_{12} in pernicious anemia, sprue, and other conditions, J. Lab. and Clin. Med. **44**: 767, 1954.
5. Glass, G. B. J.: Intestinal absorption and hepatic uptake of vitamin B_{12} in diseases of the gastrointestinal tract, Gastroenterology **30**: 37, 1956.

6. Halsted, J. A., Swendseid, M. A., Lewis, P. M., and Gasster, M.: Mechanisms involved in the development of vitamin B_{12} deficiency, Gastroenterology **30**: 20, 1956.
7. Doscherholmen, A., and Hagen, P. S.: Absorption of Co^{60} labelled vitamin B_{12} in intestinal blind loop megaloblastic anemia, J. Lab. and Clin. Med. **44**: 790, 1954.
8. Glass, G. B. J.: Differentiation of macrocytic anemias and detection of pernicious anemia and sprue in remission by accelerated measurement of hepatic uptake of radioactive Co^{60} B_{12}, International Society of Hematology, VI Congress, p. 251, 1956.
9. Turnbull, A.: Experiences with labelled vitamin B_{12}, Proc. Roy. Soc. Med. **47**: 42, 1954.
10. Halsted, J. A., Lewis, P. M., and Gasster, M.: Absorption of radioactive B_{12} in the syndrome of megaloblastic anemia associated with intestinal stricture or anastomosis, Am. J. Med. **20**: 42, 1956.

STUDIES IN HODGKIN'S SYNDROME. XII. HEREDITARY AND EPIDEMIOLOGIC ASPECTS *

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IN a group of 440 patients with biopsy-confirmed diagnosis of Hodgkin's disease and treated in The Ohio State University and University of Oklahoma Health Center Clinics (1939–1955), the familial incidence of multiple lymphomata has been found to be greater than is reported in previous similar series. The excellent review by Mazar and Straus [1] of the marital and familial incidence of Hodgkin's disease has summarized most of the published cases in which two or more members of one family have had Hodgkin's disease, and includes those families previously reported by Hoster [2] from this clinic. These families, and those published in the foreign and recent American literature in which confirmation of the diagnosis was adequate, are summarized in table 1.

It is not within the scope of this report to present a detailed analysis of the voluminous bibliography on the etiology and pathology of Hodgkin's disease. The attempts to define precisely the histopathology and etiology of Hodgkin's disease have been ably discussed by Wallhauser,[16] Jackson and Parker,[17] Hoster and Dratman,[2] and Mazar and Straus.[1] The original group of seven patients described clinically by Hodgkin [18] in 1832, and having in common lymph node enlargement, cachexia and fatal termination, included three cases which were accepted by Fox [19] as having the disease which bears Hodgkin's name. Various investigators later described individual aspects of the histopathology, but it was Sternberg's [20] analysis, in 1893, of the microscopic cellular detail, more particularly of the giant cells, and the classic description of the granuloma cell-types by Reed [21] in 1902, which formulated the diagnostic criteria for the so-called classic Hodgkin's cells. Unless otherwise stated, it is the criteria of these investigators and later of Jackson and Parker [17] which have been used in the diagnosis of the patients to be discussed.

CLINICAL DATA

A careful study of the charts of approximately 400 patients treated for Hodgkin's disease at The Ohio State University Health Center and of ap-

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TABLE 1

Cases from the Literature

	Date	Investigator	Patients
1.	1886	Degen[1]	Brother and sister
2.	1897	Murray[1]	Father and his children
3.	1903	Senator[1]	2 brothers
4.	1905	Peacocke[1]	2 brothers (twins)
5.	1914	Bunting and Yates[1]	2 brothers
6.	1919	Reuker, cited by Müller[3]	Mother and daughter
7.	1922	Galloway[1]	Father and daughter
8.	1925	Allan and Blacklock[1]	2 brothers
9.	1926	Arkin[1]	Father, son and nephew
10.	1926	Priesel and Winkelbauer[1]	Mother and daughter (infant)
11.	1926	Burnam[1]	Uncle and nephew
12.	1926	Burnam[1]	2 brothers
13.	1930	Koranyi[1]	2 brothers
14.	1933	Branch[1]	Mother and daughter (infant)
15.	1933	Chiari, cited by Branch[1]	Mother and daughter (infant)
16.	1933	Petri, cited by Morowitz[4]	2 brothers
17.	1934	Desjardins[1]	Brother and sister
18.	1934	Leutkins, cited by Remde[5]	Mother and infant
19.	1934	McHeffey and Peterson[1]	2 brothers
20.	1934	Gordon, Gow, Levitt, Weber[1]	Mother, daughter (and father?)
21.	1934	Kaplan[1]	Father and son
22.	1934	Smith and Quilligan[1]	Brother and sister
23.	1934	Uddstromer[1]	2 sisters and cousin
24.	1934	Smith and Chapman[1]	2 sisters and cousin (female) and great-uncle
25.	1936	LaPorte[6]	Father and daughter
26.	1936	Morowitz[4]	Father and son
27.	1936	Heussi[7]	Mother and daughter
28.	1936	Warner[1]	2 sisters
29.	1939	Gilbert[1]	Brother and sister
30.	1940	Hoster[1]	Father and son
31.	1942	Müller[2]	2 brothers
32.	1946	DeCandia[8]	Mother and daughter
33.	1946	Charache[1]	Mother and daughter
34.	1947	Jackson and Parker[1]	3 brothers and sister
35.	1948	Pflander[9]	Brother and sister
36.	1948	Craver[1]	Brother and 3 sisters
37.	1948	Davis[1]	Mother and daughter (infant)
38.	1950	Bonati[10]	2 brothers
39.	1950	Craver[1]	Mother and daughter
40.	1950	Remde[5]	Twin sisters (identical)
41.	1950	Sandick[11]	Father and daughter
42.	1950	Mazar and Straus[1]	Husband and wife (and son?)
43.	1951	Mazar[1]	Nephew, great-uncle, third cousin
44.	1951	Straus[1]	2 half-brothers (maternal)
45.	1954	Schier[12]	2 brothers and nephew
46.	1954	Schier[12]	Father, daughter and uncle
47.	1955	Videbaek[13]	2 brothers
48.	1956	Brennan[14]	Husband and wife
49.	1956	Weinstein[15]	2 sisters

proximately 40 patients seen at The University of Oklahoma Medical Center has produced 16 families on whom the records were felt to be accurate enough to include in table 2. Each of these families shows two or more members with Hodgkin's disease or with Hodgkin's granuloma in one and some other type of lymphoma in another relative. Of the 400 patients at The Ohio State University, a little less than half were available for interview personally by the authors in preparing this study, but such personal inter-

TABLE 2

Cases of DeVore and Doan, 1955

1. Father and son
2. Uncle and niece
3. Brother and sister, female paternal cousin and son of paternal cousin
4. Mother and son
5. Brother and sister
6. Father, son, son's paternal great-uncle and male maternal cousin
7. Male and male maternal cousin of his father
8. Two sisters
9. Niece and aunt
10. Father and daughter
11. Father and 2 sons (half-brothers)
12. Brother and sister
13. Father and daughter
14. Aunt, nephew (son of brother), great-nephew (grandson of second brother)
15. Father and son
16. Man and wife

views were the first-hand source of the family history in all but two of the proved cases.

Brief summaries of the case histories follow which illustrate the variable age range and duration of response to therapy of Hodgkin's disease in the families listed in table 2. Complete histories on all patients are available in the authors' files.

CASE REPORTS

Family 1. Hoster and Dratman [2] previously reported a man who was diagnosed at 27 years of age as having Hodgkin's disease. His father had died at the age of 33 years with the same disease. The patient, one of a group treated at The Ohio State University, died at the age of 38.

Family 2. A 24 year old white female, whose biopsied cervical lymph node revealed the typical pathologic picture of Hodgkin's disease, was treated with x-ray therapy and nitrogen mustard intravenously over a period of 13 years and was asymptomatic at the last examination (1953).

Ten years after the patient's diagnosis was made her 61 year old maternal uncle developed adenopathy involving the cervical and mediastinal nodes. Following a diagnosis of Hodgkin's granuloma by biopsy,[22] he responded well to x-ray therapy, remained well for two years, and then died unexpectedly as a result of a cerebral vascular accident.

Family 3. A 33 year old white male received x-ray therapy following a diagnosis by biopsy of a right supraclavicular node. Except for occasional x-ray treatment for recurrent adenopathy he has been clinically well for six years.

The patient's sister, at 20 years of age, had multiple biopsies [23] which confirmed the diagnosis of Hodgkin's disease. She had a spontaneous remission for 16 months, then had a recurrence of Hodgkin's disease and, after an 18-month illness, died at 22 years of age.

A second relative of the patient, a 34 year old female maternal cousin, had a cervical node biopsy, the results of which were typical of Hodgkin's disease.[24] Following x-ray therapy over the areas of involvement, the patient had been asymptomatic for 13 years at the time of the last report.

The son of a second maternal cousin, a 15 year old white male, had the diagnosis of generalized Hodgkin's disease confirmed by biopsy.[24] There was poor response to

therapy, and the patient died one year later. It is of interest that this boy's mother's maternal cousin, who was not related to other members of the family in this report, died at 16 years of age with proved Hodgkin's disease.

Family 4. A 28 year old white male with symptoms and signs of generalized Hodgkin's disease had an epitrochlear lymph node biopsy which revealed only chronic lymphadenitis. On exploratory laparotomy a common iliac lymph node biopsy was obtained with findings typical of Hodgkin's disease. He responded for a brief period to intravenous nitrogen mustard therapy, but within three months was admitted to another hospital and died shortly thereafter.

The patient's mother, a 62 year old white female with a history of adenopathy first noted three years previously, had a biopsy which revealed Hodgkin's disease. The mother responded well to x-ray and nitrogen mustard therapy for the next 18 months, then developed hemolytic anemia which responded well to cortisone therapy.

Family 5. A 32 year old white female, with a history of chills and fever for five years, had an exploratory laparotomy which resulted in biopsy of the liver and a lymph node with a diagnosis of Hodgkin's disease. She responded briefly to nitrogen mustard therapy on two occasions, but died six months later with generalized Hodgkin's disease.

The patient's brother, at 27 years of age, gave a history of cervical adenopathy and fever of three months' duration. He had a cough with expectoration of purulent material. An enlarged spleen was felt, and x-ray examination revealed a tumor in the right chest which was not thought to be accessible for a biopsy. The clinical history and the response to x-ray therapy prior to his death were considered by his physicians [25] to be diagnostic of Hodgkin's disease. Because some form of lymphoma seemed apparent from the records, and the diagnosis in the sister was by biopsy, this case has been accepted despite the absence of tissue confirmation.

Family 6. A 32 year old white male, whose axillary node biopsy was diagnostic of Hodgkin's disease, was asymptomatic for 16 months after x-ray therapy. He developed generalized Hodgkin's disease and died 22 months after first being seen.

The patient's father was first seen [26] at 40 years of age with a history of cervical adenopathy of one year's duration. Six weeks before he was seen, x-ray therapy was given over the cervical nodes, with marked reduction in swelling. Biopsy of a right cervical lymph node at that time was reported as showing atypical granulomatous features and was thought to be compatible with tuberculosis. A review of the biopsy specimen by the authors revealed no features typical of tuberculosis, but rather the characteristics compatible with Hodgkin's granuloma tissue modified by the recently administered x-ray therapy. The family of the patient stated that after the biopsy, and an apparently good response to x-ray therapy, the length of the remission and the subsequent course of his illness were almost identical to those of his son.

The patient's maternal grandfather's brother, first seen [27] at 72 years of age, was having difficulty in swallowing due to bronchotracheal adenopathy. Following x-ray therapy he was asymptomatic for eight years and then developed generalized adenopathy. After a diagnosis of Hodgkin's disease was made, he responded for six months to x-ray therapy. He then had a recurrence of abdominal and inguinal adenopathy, and died at home six months later with no further therapy. A tissue biopsy was not available for review by the authors.

Many other malignancies were reported in the patient's father's family. A second brother of the grandfather died in old age following a biopsy diagnosis of "undifferentiated carcinoma of the mediastinum," which responded only briefly to x-ray therapy.

A maternal cousin, the son of a sister of the patient's mother in whose family no other lymphomata and no malignancies have been reported, was the patient's playmate during childhood. At 27 years of age he developed adenopathy which increased in size for 18 months, during which time he showed increasing signs and symptoms of generalized Hodgkin's disease. A biopsy confirmed the diagnosis. The patient died two years later, having responded poorly to x-ray therapy. An autopsy confirmed the diagnosis of generalized Hodgkin's disease.

Family 7. A 35 year old white male had a history of left cervical adenopathy diagnosed by biopsy 18 months previously.[28] Following x-ray therapy he had been asymptomatic. He developed recurrent bouts of fever, each lasting four or five days. When no adenopathy could be found, nitrogen mustard therapy produced a clinical remission, which had lasted 18 months at the time of his last examination.

A maternal cousin of the patient's father developed supraclavicular lymphadenopathy at 51 years of age, which on biopsy a year later was diagnosed by Dr. Fred Stewart [29] as Hodgkin's disease and classified by two other outstanding pathologists as a lymphoma. Following a cachectic course with repeated x-ray treatments the patient died a year later. Other members of the family were noteworthy for their longevity, with development of cardiovascular-renal disease late in life.

Family 8. A 38 year old female with a history of cervical adenopathy of five months' duration was reported, after biopsy, as having "possible Hodgkin's disease." When axillary and inguinal adenopathy developed, a review of the original biopsy slides confirmed the diagnosis of Hodgkin's disease and x-ray therapy was given.[26] Four years later she was asymptomatic and no adenopathy could be found.

Her sister, a 28 year old female with a history of cervical adenopathy for nine months, had a cervical node biopsy diagnosed as "malignant lymphoma." A second node was biopsied [26] and diagnosed as hyperplasia due to inflammation. Despite x-ray therapy she had frequent recurrence of her adenopathy, and increasing difficulty with breathing, and died a year later with a clinical diagnosis of Hodgkin's disease. Review of the biopsy confirmed the diagnosis of a lymphoma, but more specific differentiation was not possible on the available slides.

Family 9. A 25 year old white female developed swelling and tenderness in the right supraclavicular region five months prior to a biopsy diagnosis of Hodgkin's disease. X-ray therapy had produced resolution of the node with no recurrence when she was last examined two years later.

The patient's aunt at 25 years of age developed superficial cervical adenopathy which was biopsied and diagnosed as Hodgkin's disease. Her physician reported that, with intermittent x-ray therapy, nitrogen mustard and cortisone, the patient's disease had been well controlled and that when he last examined her she was in good health after 11 years of treatment.

Family 10. A 34 year old white female had developed a chronic productive cough at 29 years of age. A mediastinal mass had been found and a biopsied supraclavicular node was diagnosed as Hodgkin's disease.[30] With x-ray and nitrogen mustard therapy she had done well for five years, but with a briefer remission after each course of therapy. She then failed to respond to the final treatment with intravenous nitrogen mustard and died at her home three months later.

The patient's father was first seen at 60 years of age, when a left axillary node was biopsied [30] and a diagnosis of reticulum cell sarcoma was made. Although the biopsy slides were not available to the authors, the diagnosis was confirmed by Dr. Lauren V. Ackerman. The patient responded poorly to treatment and died four months before his daughter, less than a year after developing symptoms.

Family 11. A 37 year old man with a history of right lower quadrant pain, right inguinal adenopathy, and occasional night sweats and fever for 16 months had an inguinal node biopsy, since no other regional nodes were of adequate size to be of significance. A diagnosis of "malignant" lymphoma was made by one pathologist, and Hodgkin's disease by a second. The authors had the slides reviewed by two other pathologists, both of whom confirmed the diagnosis of "malignant" lymphoma, one calling it a lymphosarcoma, the other not stating the type of lymphoma. Despite these findings, and with no other therapy, the patient was living and well eight years later.

The patient's father had died at 52 years of age, the clinical course and response to x-ray therapy during his terminal illness having been typical of a lymphoma. Biopsy by his physician [31] was not possible because of previous x-ray therapy. His son, the half-brother of the above patient, had died of Hodgkin's disease at 22 years of age, having failed to respond to x-ray therapy after a biopsy [31] had confirmed the diagnosis.

Family 12. A 45 year old man gave a history of having developed cervical adenopathy which 15 months before had been biopsied and a diagnosis of Hodgkin's disease made. With x-ray therapy he had responded well and required no further therapy.

The patient's sister, a 25 year old white female, had a growth removed from the anterior chest wall. Three months later, review of the slides confirmed the diagnosis of Hodgkin's disease. Following x-ray therapy there was regression of all palpable tumor tissue, and the patient was clinically well 15 months later.[32]

Family 13. A 23 year old white female, after 15 months of symptoms, had a diagnosis of Hodgkin's disease made on an excised mediastinal tumor. Despite repeated courses of x-ray therapy, the chest lesion failed to respond and she died 11 months later. An autopsy confirmed the diagnosis and revealed extensive involvement of the mediastinum and the right lung and pleural cavity. An infant, delivered during her illness, developed normally and was clinically well at two years of age.

The patient's father, a 51 year old white male, had developed generalized lymphadenopathy six months before being seen in our clinic. Biopsy of a cervical node had revealed giant follicular lymphoblastoma. On examination he had generalized adenopathy, pleural effusion and ascites, and an enlarged liver and spleen. The pleural fluid was aspirated and the sediment studied, with a diagnosis of lymphosarcoma. He responded well to nitrogen mustard and x-ray therapy for eight months. Despite x-ray therapy and a laminectomy for a lesion which then developed in the lumbar spine, the patient failed to respond to therapy and died nine months after recurrence of his illness. At the time of laminectomy, tumor tissue was found to replace the lower lumbar vertebrae and a biopsy revealed reticulum cell sarcoma and areas of fibrosis consistent with late radiation changes.

Family 14. A 50 year old white female died with Hodgkin's disease. Her physician is no longer living and records are not available, although a positive diagnosis was made by biopsy at that time. Since there are physicians in the family, the diagnosis is considered by the authors to be accurate. Malignancies were found in many other members of the family. She had no children of her own. The son of one brother and the grandson of a second brother have subsequently died with Hodgkin's disease and their cases are presented. Her nephew, a man in his twenties, died after treatment for several months with x-ray therapy. An autopsy revealed Hodgkin's disease in the lungs, liver, kidneys, spleen, prostate and retroperitoneal lymph nodes.[33]

The grandson of her second brother, a 23 year old male, developed a stiffness and soreness in the lower back, followed by fever. Examination revealed right cervical

adenopathy which, on biopsy, was diagnosed as Hodgkin's disease. He developed generalized disease, which failed to respond to nitrogen mustard and x-ray therapy except for a brief period, and died within a year.[34]

Family 15. An 18 year old white male gave a history of left supraclavicular adenopathy for six months before a diagnosis of Hodgkin's disease was made by biopsy of one node and later confirmed by an excisional biopsy of the area involved. Following demonstration of mediastinal and retroperitoneal adenopathy, a six-month remission has been produced by nitrogen mustard therapy.

The patient's father was first seen 12 years before the development of the patient's symptoms.[35] Following confirmation of the diagnosis by biopsy of a cervical lymph node, he was treated with x-ray therapy for disseminated Hodgkin's disease for three years before his death.

The brother of the patient's father was said by his widow to have died with Hodgkin's disease two years before the biopsy of the father. No medical records are available to confirm the presence of the disease in the uncle.

Family 16. A 26 year old white female gave a history of x-ray therapy for 18 months after biopsy diagnosis of Hodgkin's disease. An emergency laminectomy had to be performed at the end of this period because of the neurologic lesions resulting from involvement of the sixth and seventh cervical vertebrae, and biopsy of the involved area confirmed the diagnosis. She responded temporarily to nitrogen mustard and x-ray therapy, but the symptoms recurred and she died four months later.

The patient's husband had a diagnosis of Hodgkin's disease at 30 years of age confirmed by a biopsy obtained seven months prior to the patient's first symptom. Despite x-ray therapy and nitrogen mustard therapy, which produced temporary remissions, he failed to respond adequately to therapy and died 16 months later. A careful check of the family histories of the two patients indicated that there was no blood relationship between the two, although both families had lived in the same small town for several generations.

In addition to the families in which the diagnosis of Hodgkin's disease or other lymphoma has been verified and well established, the patients whose histories are summarized in table 3 provided only the very good history of more than one member in the family having a lymphoma. The very suggestive available data in these families follow:

Family 17. A 34 year old white male was first seen seven years after a biopsy which was diagnostic of Hodgkin's disease. He has responded well to occasional courses of x-ray therapy for 16 years since the original diagnosis. He stated that after the diagnosis had been made his mother, who has since died, informed him that his father had died in 1915 with growths in the neck and axilla which were diagnosed following surgery as Hodgkin's disease. The records and biopsy specimens of the hospital in which the patient's father was treated have been destroyed, so that tissue confirmation of the diagnosis has not been possible.

Family 18. A 29 year old man had a lymph node biopsy at The Ohio State University which showed typical Hodgkin's disease. He gave a history of his maternal grandfather's having died with Hodgkin's disease, but the physician's records and the death certificate could not be located.

Family 19. A 32 year old man had a lymph node biopsy which was interpreted as being typical of Hodgkin's disease. At the same time a sister was having similar signs and symptoms and his mother had a large right axillary mass, but neither would consent to biopsies.

Family 20. A 59 year old woman had a lymph node biopsy interpreted by three examiners as reticulum cell sarcoma, Hodgkin's sarcoma, and lymphosarcoma, respectively. Two weeks later her 63 year old sister, who had experienced low grade fever, anorexia, slight cough and malaise for a period of one year, was examined. During that year intermittent chills, night sweats and fever had developed and had failed to respond to any form of antibiotic. An exploratory laparotomy was performed, during which an enlarged spleen was removed and biopsies from the liver and lymph nodes were obtained. The spleen and liver were not diagnostic. The lymph nodes were reported by the same three examiners as above as showing giant follicular lymphoma, atypical Hodgkin's disease, and hyperplasia secondary to chronic inflammation. The patient responded to a course of nitrogen mustard therapy. When minor symptoms developed a few months later, maintenance therapy with triethylene melamine was effective. Further confirmation of the diagnosis in this patient must await future developments.

Family 21. A young adult male was admitted to University Hospital and a biopsy diagnosis of Hodgkin's disease was made. He gave a history of a "blood relative's" having had Hodgkin's disease, confirmed by biopsy, but no medical records could be obtained and the exact relationship of the "relative" could not be ascertained from the patient or his immediate family.

Family 22. A 45 year old man was seen in the Veterans Administration Hospital in Oklahoma City with cervical, mediastinal and abdominal adenopathy. A biopsy revealed reticulum cell sarcoma. His father had died in 1926 with what was reported to be Hodgkin's disease. A flood has since destroyed all of the records of the hospital in which he died, as well as the office records of the physician who treated him.

The lack of first-hand tissue confirmation of the diagnosis in each member with suggestive signs in such families prevents their use for bona fide statistical purposes, but if they are excluded from the series, this, too, may give a false impression.

The patients who were questioned personally gave histories of possible exposure to Hodgkin's disease followed by development of the disease.

A physician who developed Hodgkin's disease reported that his mother-in-law had died with Hodgkin's disease a number of years before. A 14 year old boy developed cervical adenopathy in 1948, soon after the death of a man who had served as his companion and adviser after the death of the boy's father. The man had Hodgkin's disease proved by biopsy. A 55 year old woman developed adenopathy about the time her sister's husband died with Hodgkin's disease. She had helped nurse the patient during his illness.

Discussion

The extremely variable pathologic picture and the "toxic," febrile, remitting but usually ultimately fatal clinical course of Hodgkin's disease have resulted in keen speculation concerning its etiology. Hoster and Dratman [2] first summarized and then considered in detail the reasoning resulting in the several hypotheses that Hodgkin's disease is: (1) a neoplasm; (2) an inflammatory reaction; (3) a transition stage between an inflammation and a neoplasm, or (4) a metabolic abnormality.

Although the malignant character of fully established progressive Hodgkin's disease is rarely questioned, the hypothesis that the etiology of Hodg-

kin's disease is that of other malignancies has received little support in publications appearing since Hoster's review. Dreyfus [36] stated that the granuloma of Hodgkin's disease is a sign of the defensive reaction of the organism against cancer. Moeschlin and Swartz,[37] from the study of smears of lymph glands and spleen from 65 patients having Hodgkin's disease, concluded: "Hodgkin's cells should be regarded as tumor cells because: (1) Transition forms from reticulum cells to Hodgkin's cells were never found; (2) All Hodgkin's cells showed typical big nucleoli of tumor nature; and (3) Hodgkin's cell mitoses differed greatly from reticulum cell mitoses."

Inflammatory reactions (fever, eosinophilia, increased sedimentation rate) were interpreted as a result of pathologic proteins and sensitization of the body thereto. The authors presented data on three patients treated by radical excision of affected lymph nodes, followed by intensive radiation, with clinical cures of from seven to nine years. Such a response was considered to be typical of that of a malignant tumor rather than of an inflammatory or metabolic abnormality. Many similar cases of prolonged therapeutic response have been reported in the literature. Stewart and Doan [38] have reported a series of 23 patients from Memorial Hospital, New York, originally diagnosed as Hodgkin's granuloma from lymph node biopsies read by Ewing himself, four of whom survived in good health with occasional irradiation therapy for six, 10, 17 and 25 years, respectively. Van der Werff [39] discussed 25 patients, including two of his own, in whom surgical extirpation, intensive radiation or a combination of the two methods resulted in remissions lasting from five to 27 years. Bernard and Ossipovski [40] reported cases clinically well after 11, eight, and six years following surgery. Lövgren and Törnquist [41] reported two cases of Hodgkin's disease of the gastrointestinal tract well after four and one-half and 13 years, respectively, following surgery and radiation therapy.

The findings of Moeschlin and his co-workers have been refuted by Hoffman and Rottino,[42] who have described and documented the transition from reticulum cells to Hodgkin's cells. The degree of "malignant appearance" of the cells varies from patient to patient, and in one patient during the course of the disease from nearly normal, typical reticulum cells to "malignant cells" which display many nucleoli and atypical forms. The fact that some patients have prolonged remissions following local intensive therapy by surgery or x-radiation may apply to the control of a local inflammatory lesion as well as to malignancy.

The statistics compiled by Hoster [43] on the incidence and distribution of Hodgkin's disease indicate that reported cases tend to parallel in number and distribution the reported incidence of other malignancies. He found no evidence of endemic areas, such as those seen with infectious diseases, but he did not consider his statistics to be conclusive in ruling out an infectious origin.

No valid clinical or experimental data support the second or fourth hy-

potheses presented by Hoster,[2] that Hodgkin's disease is a simple infection or a primary metabolic disease.

Clinical and experimental data have yielded increasing evidence that there may be a virus-like agent, which is the exciting factor, which may ultimately result in the induction of Hodgkin's disease in individual patients in families in whom there is a reticuloendothelial system susceptible to such an irritative metamorphosis.

The question as to whether Hodgkin's disease may be transmissible from man to man was first raised by Obratzow [44] and later by Horder [45] who described the inoculation of three individuals in whom Hodgkin's disease later developed in the adjacent lymph node area. Mazar and Straus [1] described one family of husband and wife from the literature, and another of their own, in whom Hodgkin's disease developed in both individuals at approximately the same time. A third confirmed case is reported in table 1 and a fourth in table 2 in the present series. Gow [46] also reported a husband and wife, but the presence of Hodgkin's disease was not adequately confirmed. If all five husband-and-wife combinations are accepted, they still are not adequate to indicate direct transmission of the disease, and probably, as stated by Mazar and Straus,[1] represent only a fortuitous circumstance. Other histories in the series at The Ohio State University were suggestive of possible transmission of the disease. In Family 6, in table 2, there were three members of the paternal side of one family who had Hodgkin's disease. The maternal cousin, who was a playmate of the cousin treated at The Ohio State University, gave no family history of the disease among other maternal relatives, yet he also developed Hodgkin's disease. The woman who developed Hodgkin's disease after contact with her brother-in-law, the boy who developed the disease after contact with a close neighbor and companion, and the physician whose mother-in-law had previously died of the disease, suggest the need for an investigation of the possibility of transmission following contact with other individuals having Hodgkin's disease. Macklin [47] cites the case of two medical school classmates who developed Hodgkin's disease at approximately the same time and, following similar courses, died within a few months of each other. The prolonged spontaneous remission of one of the two half-brothers in Family 2 might be postulated as due to the development of resistance to the etiologic agent.

In contrast to these few patients, who reported development of Hodgkin's disease following direct exposure to other patients, most of the patients interviewed reported no other members of the family who had Hodgkin's disease, knew of no contact with individuals who had the disease, and frequently had never heard of this disease prior to the time of their own diagnosis.

Mazar and Straus [1] point out that in five instances Hodgkin's disease has been found in an infant or newborn child of a mother with a positive diagnosis of Hodgkin's disease. Such a result would suggest placental transmis-

sion, such as that of certain breast malignancies in experimental animals. There are reported in the literature 40 instances in which normal infants have been delivered by mothers with a positive diagnosis of Hodgkin's disease, and many other such cases are known to the authors. If there is placental transmission of an infectious agent, such transmissions rarely cause Hodgkin's disease in infancy.

Experimental transmission of malignancies of virus etiology in animals indicates that there may be transmission of a disease only at certain stages of development of the animal and the virus, and that there may be a latent or incubation period of months to years before the disease becomes apparent in the recipient. Only by following the offspring of patients with Hodgkin's disease throughout their lives can the possibility of placental transmission of Hodgkin's disease be eliminated completely.

All attempts to transplant or transmit Hodgkin's disease as it is found in man to any laboratory animal have failed, making more difficult basic investigations of the disease.[48] Investigators have of necessity resorted to indirect methods of studying viruses, or have used basic research methods involving tissue culture and physical-chemical technics. Grand [49] in 1944 first described cytoplasmic inclusion bodies in tissue cultures of human lymph nodes affected by Hodgkin's disease which were not present in the cultures of normal nodes or those from diseases such as leukemia or sarcoma. His observations were not confirmed by Hoster [50] or Rottino, Worken and Hollander.[51] Jacquez and Porter [52] studied electron-micrographs of tissue cultures of Hodgkin's disease tissue and neoplastic and non-neoplastic controls. Although they stated that inability to find Sternberg-Reed cells for study made the data incomplete, they favored a nonviral etiology because of the absence of inclusions similar to known viruses. Hoster and his associates [50] analyzed electron-micrographs of macromolecular particle populations prepared by differential ultracentrifugation of lymph node homogenates. Although they reported that the predominant particle sizes differed significantly from those of neoplastic nodes, the appearance of the characteristic particles was not that of any known virus. The size of the particles, which were present in increased numbers, was about that of the poliomyelitis virus. Investigations of various physical and chemical characteristics of those particles and electron microscopy of intact elements now in progress in the Hoster Memorial Laboratories still offer no conclusive evidence concerning the presence of a possible virus.

Bostick [53] first noted a small but statistically significant increase in mean mortality of chick embryos following injection into the amniotic sac of tissue extracts from other Hodgkin's disease nodes, in contrast to extracts from other types of tumors and tissues. He has attempted a variety of methods of characterizing the responsible agent, using indirect methods of study to detect viruses. The physical characteristics of the agent, which is not encountered in any control experiments, were described.

Grand [54] confirmed his original tissue culture results in further experiments, in which he prepared a purified fraction from tissue supernatants and the pleural fluid from a patient having Hodgkin's disease. The purified fraction had a characteristic effect on cultures of chick spleen and mouse or human lymph nodes and of chick chorio-allantoic membranes. Reiman [55] and her associates noted a number of changes induced by serum from patients having Hodgkin's disease in the growth of human lymph node cultures. Although the presence of virus-like inclusions was not noted in these cultures or in cultures of Hodgkin's disease tissue, the author stated: "The Hodgkin's serum-induced changes appear to bear a qualitative resemblance to the fundamental alterations which characterize the growth of Hodgkin's explant cells in the presence of normal serum in tissue cultures." Worken and Chambers,[56] using serum from Hodgkin's patients, normal serum, and sera from patients having various malignancies and tuberculosis, demonstrated an effect with Hodgkin's sera only on the migration, activity and disintegration of the lymphocytes.

Through differential centrifugation of nodes of Hodgkin's disease, lymphosarcoma, lymphoid leukemia, and normal individuals, a purified suspension was made which would produce an antigenic reaction in rabbits only when Hodgkin's tissue was used. The degree of agglutination produced in testing the reaction was proportional to the dilution of the original serum.

In attempting to reproduce Hodgkin's disease in animals or to culture the etiologic agent, Montgomery and Foard [48] inoculated a variety of laboratory animals and culture media with suspensions of Hodgkin's tissue, with the uniformly negative results experienced by other investigators. They concluded that their failure to transmit the disease resulted from the lack of a suitable host, namely, man.

The experimental data of many investigators have "suggested" the possibility of an etiologic agent capable of reproducing itself in a manner comparable to that of a virus, but each has thus far failed to give adequate evidence of such an agent.

The evidence available from the records of families reported in table 1, from the literature, and in table 2, from the present series indicates that there is a definite familial tendency favorable to the development of lymphomas. Of the 400 charts reviewed from The Ohio State University Hospital files, an adequate, detailed and verified family history was recorded in only about one-half of the patients. The family histories had sufficiently detailed data in 40 instances from the University of Oklahoma. Among these 240 selected histories, there were a number of reports given by patients of "cancer of the liver" or some other diagnosis which had not been confirmed by biopsy or autopsy. How many of these unidentified lesions might have been lymphomas was impossible to determine. Similarly, it is impossible to determine the definitive diagnosis in relatives who were reported to have had large lymph nodes associated with their deaths 15 to 50 years previously

TABLE 3

Cases of DeVore and Doan

History of Familial Disease Without Documentary Proof

17. Father and son
18. Man and his maternal grandfather
19. Brother and sister
20. Two sisters
21. Man and "blood relative"
22. Father and son

after a clinical diagnosis of tuberculosis or other lymph node disease. Several families were found to have an apparent familial incidence of other types of malignancy.

Instability of the reticuloendothelial system was also evidenced by acquired hemolytic anemia in a third sister in the family reported by Weinstein,[15] and in the niece of a patient in the present series. The incidence in the families studied is not statistically significant of an increased incidence of malignancies or of nonmalignant diseases of the reticuloendothelial system.

Hoster's review [43] of the incidence of Hodgkin's disease in the general population indicates that 2.5 patients per 100,000 population per year is the highest possible estimate of incidence on the basis of present reported figures, which include errors of omission in diagnosis in those individuals thought to have other diseases. The highest incidence thus far reported in any single group studied is 2.27 new cases per 100,000 living persons, as found in the United States Army and Navy during 1941–1945. This predominantly young adult population comprises the group in the United States which should have a higher incidence than any other. The highest incidence in an autopsy series was 0.33% of 60,000 autopsies.[2]

Our incidence of lymphomas found in more than one member of the same family in a group of 440 patients is greater than would be accounted for on the basis of chance alone. With further investigation other families may be found, since Macklin,[47] through her careful study of the familial incidence of other malignancies, has found that, with the best of family histories obtained from the patient and the patient's immediate family by a trained geneticist or social worker, less than one third of the malignancies actually occurring in the family are recorded. The remainder are unknown to other members of the family and can be found only through a parallel review of death records and physician's records for all members of any family studied.

Even if unconfirmed histories of lymphomas or other nonspecified malignancies were included in this series, the familial incidence of Hodgkin's disease would be too low to be accounted for on the basis of dominant or recessive gene factors. The incidence does suggest, however, that in some families the reticuloendothelial system may be particularly sensitive or susceptible to the development of the lymphomas.

Twins then might, under conditions of similar environmental exposure, develop a lymphoma similar in type and at about the same age. The devel-

TABLE 4

Twins with One Only Having Hodgkin's Disease

A. 1938	Smith[1]	10 year old boy with normal twin
B. 1937	Martin and Jentsh[1]	1 girl died, other well 5 years later
C. 1940	Macklin[1]	10 year old boy with normal twin (biopsy)
D. 1946	Charache[1]	3 sets with one Hodgkin's and one normal
E. 1953	DeVore and Doan	2 sets with one Hodgkin's and one normal (not noted whether identical)

opment of Hodgkin's disease or of any other lymphoma in both of identical twins has not been recorded in the medical literature except in one family (table 3). In this series at The Ohio State University, only two sets of twins were involved. There is no record as to whether they were identical twins, but in each instance at least five years' follow-up of the normal twin revealed no evidence of the disease.

The hypothesis of a familial susceptibility of all mesenchymal tissues to lymphoma-like changes is suggested by one family in which, during the time that a father in his sixties was under treatment for Hodgkin's disease, proved by biopsy, his son developed a fibrosarcoma, confirmed by biopsy, which caused the son's death prior to the death of the father; but the absence of other similar instances or of a family history of leukemia in this series, and the rarity of such reports in the literature, apparently fail to support this hypothesis.

CONCLUSIONS

In this familial study of 440 carefully verified cases of Hodgkin's syndrome there were 15 families in which proved multiple cases of Hodgkin's disease or other lymphomata developed in blood relatives with or without direct contact, and in some instances with an interval of some years between. There were six additional families with presumptive multiple intrafamilial incidence. Although a husband and wife developed Hodgkin's disease at the same time, the clinical evidence for the disease's being directly transmissible is slight and the experimental evidence in the literature inconclusive. The epidemiology of the disease under such circumstances, with the etiology still unknown, is difficult of determination, due to the probable multiplicity of healthy "carriers" for every active case in which an infectious agent is involved. The statistical data do not support either dominant or recessive gene factors as influencing incidence and expressivity of Hodgkin's disease. The evidence does suggest that in some families the reticuloendothelial system may be more susceptible than in others to as yet undetermined and unidentified environmental factors which may precipitate the development of lymphomata.

SUMMARIO IN INTERLINGUA

Un studio familial de 440 cautemente verificate casos de syndrome de Hodgkins resultava in le detection de 17 familias in que multiple casos de demonstrate morbo de Hodgkin, o de altere lymphomas se disveloppava in consanguineos con o sin contacto directe e a vices mesmo con intervallos de plure annos. In sex familias additional il

habeva presumption de multiple incidentia intrafamilial. Ben que un marito e su marita disveloppava morbo de Hodgkin al mesme tempore, le provas clinic pro le directe transmissibilitate del condition non es forte, e le correspondente provas experimental que se trova in le litteratura non es conclusive. Sub iste conditiones e in vista del facto que le etiologia remane incognoscite, le epidemiologia del morbo es difficile a determinar, proque il es probabile que il ha un multiplicitate de portatores in bon stato de sanitate pro omne caso active in que un agente infectiose es involvite. Le datos statistic non supporta le conception que dominante o recessive factores genic exerce un influentia super le incidentia e le expressivitate de morbo de Hodgkin. Lo que es suggerite per le datos es que in certe familias le systema reticuloendothelial es possibilemente plus susceptibile que in alteres al action de non ancora determinate o identificate factores ambiental que pote precipitar le disveloppamento de lymphomas.

BIBLIOGRAPHY

1. Mazar, S. A., and Straus, B.: Marital Hodgkin's disease, Arch. Int. Med. **88**: 819–830 (Dec.) 1951.
2. Hoster, H. A., Dratman, M. B., Craver, L. F., and Rolnick, H. A.: Hodgkin's disease, 1832–1947, Cancer Research **8**: 1–78 (Jan.-Feb.) 1948.
3. Reuker quoted by Müller E. M.: Zur Frage des familiaren Vorkommens des Lymphogranulomatose, Ztschr. f. mensch. Vererb. u. Konstitutionslehre **25**: 527–538, 1941–42.
4. Morowitz, P.: Rassenhygiene und Bvolkerungspotlitik. Erbliche und konstitutionelle Faktoren bei einigen Blutkrankheiten, München. med. Wchnschr. **83**: 2073–2074 (Dec. 18) 1936.
5. Remde, W.: Über konkordantes Auftreten von Lymphogranulomatose bei einigen Zwillingen, Innere Med. **5**: 15–22 (Jan.) 1950.
6. LaPorte, D.: Maladie de Hodgkin familiale, Presse méd. **44**: 661, 1936.
7. Heussi, M.: Ueber Lymphogranulomatose besondere ihr familiäres Vorkommen, 1936, Fluntern, Zurich.
8. DeCandia, S.: Morbo di Hodgkin Familiare, Clin. nuova **2**: 234–236, 1946.
9. Pflander, U.: Lymphogranulomatose Hodgkin et disposition hereditaire, Lausanne, 1948, 68/3 (141–157).
10. Bonati, F.: Clinical and statistical findings in Hodgkin's disease, Gior. clin. med. **31**: 746–760 (June) 1950.
11. Sandick, H.: Hodgkin's disease involving the stomach, Gastroenterology **15**: 135–143 (May, part 1) 1950.
12. Schier, W. W.: Familial Hodgkin's disease, Blood **9**: 236–240, 1954.
13. Videbaek, A.: Familial Hodgkin's disease, Acta haemat. **14**: 200–202, 1955.
14. Brennan, M. J., Henry Ford Hospital: Personal communication.
15. Weinstein, A., Nashville, Tenn.: Personal communication.
16. Wallhauser, A.: Hodgkin's disease, Arch. Path. **16**: 522–562, 672–712, 1933.
17. Jackson, H., and Parker, F.: Hodgkin's disease and allied disorders, 1947, Oxford University Press, New York, p. 177.
18. Hodgkin, T.: On some morbid appearances of the absorbant glands and spleen, Med. Chir. Tr., London **17**: 68–114, 1832.
19. Fox, H.: Remarks on the presentation of microscopic preparations made from some of the original tissue described by Thomas Hodgkin, 1832, Ann. Med. Hist. **8**: 370–374, 1926.
20. Sternberg, C.: Über eine Eigenartige unter dem Bilde der Pseudoleukämie Verlaufende Tuberculose des lymphatischen Apparates, Ztschr. f. Heilk. **19**: 21–90, 1898.
21. Reed, D. M.: On the pathological changes in Hodgkin's disease with special reference to its relation to tuberculosis, Johns Hopkins Hosp. Rep. **10**: 133–196, 1902.
22. The Holzer Clinic, Gallipolis, Ohio: Personal communication.

23. Dr. Andre Crotti, Columbus, Ohio: Personal communication.
24. Dr. Esther Marting, Cincinnati, Ohio: Personal communication.
25. Cleveland Clinic: Personal communication.
26. Mayo Clinic: Personal communication.
27. Lima Memorial Hospital, Lima, Ohio: Personal communication.
28. Philadelphia Naval Hospital: Personal communication.
29. Dr. Fred Stewart, Memorial Hospital, New York, N. Y.: Personal communication.
30. Barnes Hospital, St. Louis, Missouri: Personal communication.
31. Pack Medical Group, New York, N. Y.: Personal communication.
32. Dr. Everett Sugarbaker, Jefferson City, Missouri: Personal communication.
33. Veterans Administration Hospital, Muskogee, Oklahoma: Personal communication.
34. Walter Reed Hospital, Washington, D. C.: Personal communication.
35. Dr. Albert E. Winston, Steubenville, Ohio: Personal communication.
36. Dreyfus, B.: Maladie de Hodgkin et reticula-sarcomatose, Le Sang, Biol. et Path. (Paris) **19**: 316–318, 1948.
37. (a) Moeschlin, S., Swartz, E., and Wang, H.: Die Hodgkinzellen als Tumorzellen, Schweiz. med. Wchnschr. **80**: 1103–4, October 14, 1950.
(b) Hodgkin cells as tumor cells, International Society of Hematologists, Third International Congress, pp. 266–272, 1950.
38. Stewart, F. W., and Doan, C. A.: An analysis of the lymphadenopathy question with special reference to Hodgkin's disease and tuberculosis, Ann. Surg. **93**: 141–152, 1931.
39. Van der Werff, J. T.: Long remissions in Hodgkin's disease, Acta radiol. **33**: 31–40 (Jan.) 1950.
40. Bernard, J., and Ossipovski, B.: Le traitement chirurgical de la maladie de Hodgkin, Semaine d. hôp. Paris **25**: 3503–3508, 1949.
41. Lövgren, O., and Törnquist, S.: Isobrad Lymfogranulomatos i magtarmkanalen, Nord. med. **39**: 1505–1506, 1948.
42. Hoffman, G. T., and Rottino, A.: Phase microscopy studies of Hodgkin's disease lymph nodes in relation to histogenesis of the Sternberg-Reed cell, Blood **5**: 74–78 (Jan.) 1950.
43. Hoster, H. A.: Studies in Hodgkin's syndrome: a distribution study of Hodgkin's disease in the United States, Ohio J. Sc. **44**: 245–250, 1944.
44. Obratzow, L. G., quoted by Murray *in* Allbutt's System of medicine, 1897, The Macmillan Company, New York, pp. 573–596.
45. Horder, T.: A clinical concept of lymphadenoma or Hodgkin's disease, *in* Rose research on lymphadenoma, 1932, John Wright & Sons, Ltd., Bristol, England, pp. 1–6.
46. Gordon, M. H., Gow, A. E., Levitt, W. M., and Weber, F. P.: Recent advances in the pathology and treatment of lymphadenoma, Proc. Roy. Soc. Med. **28**: 1035–1050, 1933–34.
47. Macklin, M. T.: Personal communication.
48. Montgomery, P. O'B., and Foard, T. B.: Experimental attempts to transmit Hodgkin's granuloma, Texas Rep. Biol. and Med. **10**: 53–58 (Spring) 1952.
49. Grand, C. G.: Tissue culture studies of cytoplasmic inclusion bodies in lymph nodes of Hodgkin's disease, Proc. Soc. Exper. Biol. and Med. **56**: 229–230, 1944.
50. Hoster, M. S., Van Winkle, Q., Rabatin, J. G., and Hoster, H. A.: Macromolecular particles obtained from human neoplastic and non-neoplastic lymph nodes, Cancer Research **12**: 69–74 (Jan.) 1952.
51. Rottino, A., Worken, B., and Hollender, A.: A study of the behavior in tissue culture of lymph nodes from Hodgkin's disease, Am. J. Path. **24**: 669–670 (May) 1948.
52. Jacquez, J. A., and Porter, K. R.: Electron microscopy observations on Hodgkin's material, Cancer **2**: 853–856 (Sept.) 1949.
53. (a) Bostick, W. L.: The serial passage of Hodgkin's disease extract in chicken eggs, J. Immunol. **59**: 189–193 (June) 1948.

(b) Bostick, W. L.: Virus interference by serially passed Hodgkin's disease extracts in chicken eggs, Proc. Soc. Exper. Biol. and Med. **74**: 519–521, 1950.
(c) Bostick, W. L., and Hanna, L.: Experimental studies of the etiology of Hodgkin's disease, Cancer Research **11**: 505–510 (July) 1951.
(d) Bostick, W. L., and Hanna, J. L.: Characteristics of a virus isolated from Hodgkin's disease tissues, Proc. Am. A. Cancer Research **2**: 6 (Apr.) 1955.
(e) Bostick, W. L.: Serial intracranial passage of Hodgkin's disease material in suckling mice, Federation Proc. **13**: 424 (Mar.) 1954.
54. (a) Grand, C. G.: The production of agglutinins in rabbits by injections of purified extracts of biopsied Hodgkin's lymph nodes, Cancer Research **10**: 221, 1950.
(b) Grand, C. G.: Purification and physical properties of the active agent in Hodgkin's disease, Unio. Internationalis Contra Cancrum **6**: 1292–1294, 1950.
55. Reiman, M. S., Stern, I. R., Ford, M. Z., and Hoster, H. A.: Studies in Hodgkin's syndrome, influence of normal serum and Hodgkin's serum on cellular growth and morphology in tissue culture, Cancer Research **10**: 467–473 (Aug.) 1950.
56. Worken, B., and Chambers, R.: Effect of Hodgkin's disease blood serum on lymphocytes of normal mouse lymph nodes in tissue culture, Cancer Research **10**: 250 (Apr.) 1950.

CHRONIC, DISSEMINATED, NONLIPOID RETICULOENDOTHELIOSIS (HISTIOCYTOSIS X): TREATMENT WITH CORTICOTROPIN AND ANTIBIOTICS, WITH REPORT OF TWO CASES *

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DURING the last few years occasional reports have appeared in the literature concerning a group of diseases of the reticuloendothelial system which have the appearance of inflammatory granulomas and are thought to be of infectious origin, although the etiology is still unknown. They have many of the characteristics of neoplasms, but they are not true tumors, since they grow by the addition of cells and not by cell division.

European investigators [1] had previously called attention to the intimate relationship between eosinophilic granuloma of bone, Hand-Schüller-Christian disease and Letterer-Siwe disease as interrelated manifestations of the same fundamental pathologic process. But it is to Lichtenstein [2] that we owe the expression "histiocytosis-X" as a broad general designation for this group of reticuloendothelioses. This relationship is clearly shown in tables 1 and 2, which are used here with the author's permission. It will be seen that this group of related diseases, with widely varied manifestations, may now be classified under the single heading of histiocytosis-X, and still be sufficiently differentiated that useful therapeutic and prognostic distinctions can be made.

Bierman [3] in 1952 reported upon the ameliorative effects of a combination of antibiotics (chlortetracycline, chloramphenicol and penicillin) in a pair of identical twins with Letterer-Siwe disease. Penicillin alone, or with streptomycin, had no effect, nor did x-ray therapy. As a matter of fact, radiation made the lesions more serious in one of twins to whom it was given. Later on this twin received the combination of antibiotics, and also improved. Bierman comments that this is the first reported occurrence of this disease in identical twins since Letterer's original description in 1924,[4] and that Siwe [5] believed the illness to be nonhereditary. The favorable effect of the combined (broad-spectrum) antibiotic therapy suggests that the etiologic agent might be a hitherto undiscovered infectious one.

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In 1951 Blahd [6] reported a case of Hand-Schüller-Christian disease in an adult patient who was unsuccessfully treated with cortisone after starting treatment with ACTH. The latter had to be hastily abandoned when the patient developed a severe anaphylactoid reaction after the first injection.

In 1953 Bass [7] reported upon the successful use of cortisone or ACTH in four out of five cases of reticuloendotheliosis in children. He and his co-authors concluded that in cortisone and corticotropin we have remedies which, although possibly not curative, are nevertheless of great value in the treatment of this disease. In one of their cases ACTH was actually life-saving, when given in small (8 mg.) doses by slow intravenous drip. In another case the progress of the disease seemed to have been miraculously stopped, only to return when the drug was discontinued. In one of their five cases ACTH was of no value. This was an infant with rapidly progressive Letterer-Siwe disease. However, in the Hand-Schüller-Christian cases that were severe and apparently passing into the acute (L-S) phase, ACTH proved to be of greatest value. In the more chronic (S-C) phase, cortisone seemed to be effective. The authors commented that, although they did not mean to imply that either cortisone or corticotropin cures reticuloendothelial disease, they are extremely valuable adjuncts which should be used along with other agents, such as the anti-folic acid compounds or x-ray therapy.

On the other hand, Gray and Taylor [8] in 1953 recorded the case of a child with systemic reticuloendotheliosis which progressed while under treatment with ACTH to a rapidly fatal monocytic leukemia of the Schilling type. They remarked that this case offers further evidence of the origin of the monocyte from the mesenchymal cells of the reticuloendothelial system. It was noted that others (Doniach, quoted by Gray and Taylor) had reported cases in which histiocytic reticuloendotheliosis had occasionally proceeded to monocytic leukemia while under no specific therapy.

The strictly localized form of the disease, eosinophilic granuloma of bone, was first described, and delineated as a clinical entity, by Lichtenstein and Jaffe [9] in 1940. They reported the case of a four year old girl with a single granulomatous lesion in the femur which contained numerous eosinophils. Since then many such cases of solitary or multiple osseous lesions have been recorded, many of them simulating roentgenographically the appearance of primary neoplasms.

Others have reported cases of skeletal lesions associated with pulmonary infiltrations, some of them with associated diabetes insipidus. In 1954 May, Garfinkle and Dugan [10] reported three cases of eosinophilic granuloma of the lung. Their third patient, whose pulmonary lesion was biopsied, also had diabetes insipidus and slight exophthalmos. Although his skull x-rays did not reveal any bony abnormalities, they regarded this case as an example of Hand-Schüller-Christian disease, with its triad of diabetes insipidus, exophthalmos and cranial defects, and cited the case in support of the concept that

eosinophilic granuloma and Hand-Schüller-Christian disease are fundamentally related.

In a more recently reported case, that of Childers, Middleton and Schneider [11] in 1955, definite histologic proof was obtained to support the diagnosis of eosinophilic granulomatosis of the lungs and right femur. The authors reported that response to x-ray therapy was most gratifying and in keeping with the known radiosensitivity of this essentially benign lesion, the patient having remained well for 33 months following treatment.

In view of the relative infrequency of this disease, it is extremely unlikely that any one investigator would ever accumulate a sufficient number of cases to permit a controlled study. It is for this reason that these cases are being reported.

Case Reports

Case 1. The patient, a 15 year old schoolboy, was brought to the office on April 5, 1954, by his mother because of a lump on the right side of his neck which she suspected of being mumps. There was also a soft, nontender swelling on the right forehead, which was thought to be the result of a mild accidental blow on the head suffered about a month before. He had thought nothing of it until an ordinary bruise had appeared. It was only the appearance of the swelling in the neck that prompted the patient's mother to seek medical advice.

Although there was no fever, there was a mild pharyngitis, and the patient was placed on tetracycline therapy for four days, and a skull x-ray was obtained immediately.

At first the mass on the head was thought to be merely a superficial hematoma undergoing softening and resorption, and it was the roentgenographic appearance of the skull which was most arresting (figure 1). Within 48 hours another small mass appeared just behind the right ear. There were no signs or symptoms of intracranial injury, and the patient continued to feel very well, going to school and even running a mile race. During this period of waiting for a report on the biopsy, laboratory studies and further x-rays were being made.

Past medical history was entirely negative except that at five years of age the patient had suffered a fall from a bicycle. He did not recall the extent of the injury, and there were no sequelae other than an inconspicuous scar above the right eyebrow.

The family history was interesting in that the patient was one of a pair of nonidentical twins, and there was a history of cancer in his maternal grandmother and great-grandmother.

Physical examination revealed a healthy, well nourished, alert and intelligent white male youth of 15. Temperature was normal; blood pressure, 130/80 mm. of Hg; pulse, regular, 68 per minute. The skin was normal and healthy except for the presence of the soft, fluctuating, nontender mass, about 3 cm. in diameter, at the hairline in the right frontal area. The lesion extended well above the hairline into the hair of the scalp. There was no discoloration of the skin, and the fluctuant characteristics of the swelling seemed to indicate that its contents were semifluid. The posterior cervical and auricular lymph nodes were enlarged, indurated and nontender. No other lymph nodes were involved. The lungs were clear and resonant; the heart was normal. The remainder of the physical examination was essentially normal in all respects.

An x-ray of the chest showed the lungs to be clear, and the heart, great vessels, diaphragm, pleura and bony framework were all normal.

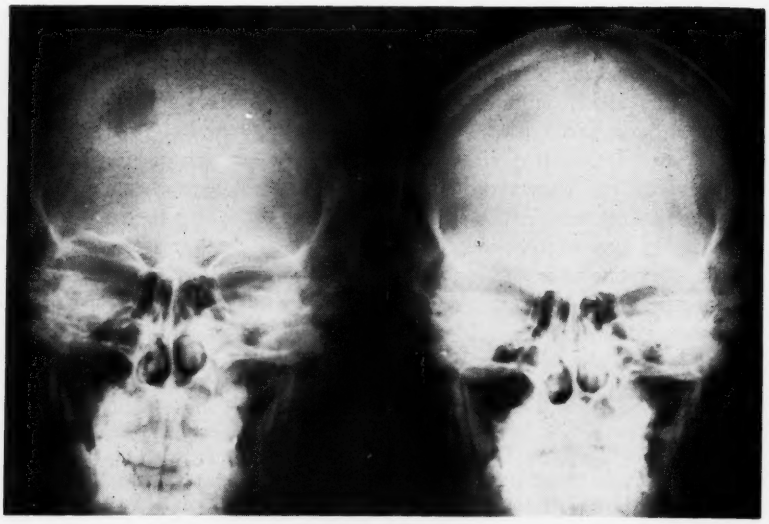

FIG. 1A. *Case 1.* X-rays of the skull: frontal views showing the appearance of the osteolytic lesion before (left) and after (right) treatment.

The skull x-ray showed a bony defect, measuring 2.7 cm. in diameter, involving the frontal bone, about 2.5 cm. to the right of the midline. The margins were ragged, but no bony sclerosis was seen about the defect. Both tables of the skull were involved, but the bone destruction was more extensive in the outer table. No other lesion of the cranium could be identified. There were no intracranial calcifications, and no skull fracture was present.

TABLE 1

Tables 1 and 2 show the integration and classification of the chronic, nonlipoid reticuloendotheliosis as histiocytosis X. (After Lichtenstein, and reproduced with the author's permission.)

Distribution of Lesions		Clinical Expressions	Age Incidence	Treatment	Prognosis
Localized in bone (one, several, or many foci); no discernible visceral involvement		Eosinophilic granuloma of bone	Infants, children, and young adults (occasionally older adults)	Curettement or x-ray therapy	Cure (although additional skeletal lesions may sometimes appear)
Disseminated	Acute or subacute course	Letterer-Siwe syndrome	Infants and young children below age of 3 years; occasional young adults (adult counterpart of L-S syndrome)	As yet nonspecific: Supportive—Antibiotics for secondary infections; x-ray therapy for skeletal and cutaneous lesions	Serious, though probably not invariably fatal; in occasional children, disease may become chronic or go into remission
	Subchronic or chronic course	Schüller-Christian syndrome (not necessarily Christian triad)	Children and young adults; occasional older adults	As for L-S syndrome; also x-ray therapy or β-hypophamine for diabetes insipidus; x-ray therapy for early pulmonary infiltration; cortisone?	Guarded, especially for children showing active progression and for patients (adults included) with pulmonary fibrosis and/or pituitary involvement

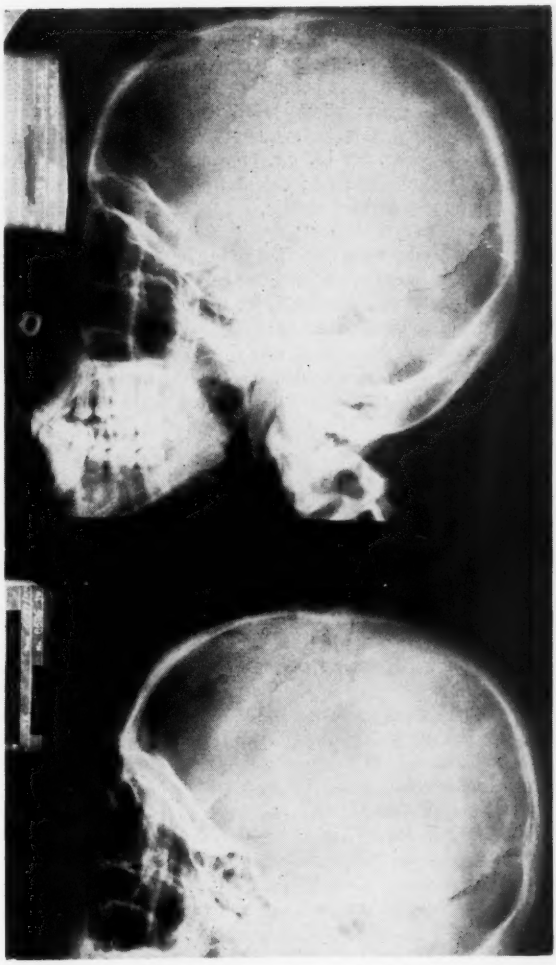

FIG. 1B. *Case 1.* Lateral views, before (above) and after (below) treatment.

TABLE 2

Classification of Histiocytosis X

Histiocytosis X, localized to bone (eosinophilic granuloma, solitary or multiple)
Histiocytosis X, disseminated, acute or subacute (L-S syndrome)
  With destructive skeletal lesions (E. G.)
  With transition to chronic phase (S-C)
Histiocytosis, disseminated, chronic (S-C syndrome)
  With destructive skeletal lesions (E. G.)
  With early extraskeletal lesions (indicate sites) resembling E. G.
  With acute or subacute exacerbation (L-S)
  With involvement predominantly of bones, lungs, pituitary, and/or brain, skin, mucous membranes (oral, anal, genital), liver or lymph nodes, etc. (in varying combinations, as the case may be)

Laboratory examinations: Blood count and urinalysis were not remarkable. Bence Jones protein was not present. Erythrocyte sedimentation rate was 32 mm. fall per hour; packed cell volume, 44 c.c.; corrected sedimentation rate (Wintrobe), 27 mm. fall per hour (the normal rate being 0 to 10 mm. fall per hour). Total serum protein was 6.2 gm. per 100 c.c.; albumin, 3.92 gm.; globulin, 2.29 gm.; albumin-globulin ratio, 1.7:1.0. There was no evidence of diabetes insipidus.

Serum calcium was 12.4 mg. per 100 c.c. (normal, 9 to 11); inorganic phosphorus, 4.8 mg. per 100 c.c. (normal, 3 to 5); calcium-phosphorus ratio 2.52:1. Alkaline phosphatase was 6.2 Bodansky units (normal, 1.5 to 4.0). These values are consistent with the presence of an osteolytic lesion.

The patient was prepared for surgery and tissue obtained for pathologic study with the help of a surgeon, the late Dr. Peter Crabtree. An incision was made over the mass in the right frontal area and carried down to the bone. A defect of about 3 cm. in diameter was found. The tumor mass was slightly larger, about 4 cm. in diameter. It was very soft, myxomatous tissue and was difficult to remove. After as much of this tissue was removed as possible, the bone edges were curetted and rongeured. The wound edges were closed with several layers of interrupted silk sutures. One of the large posterior cervical lymph nodes was then removed.

The tissue from the defect in the skull consisted of firm, grayish red, myxomatous substance showing areas of hemorrhage. That from the right cervical region was an encapsulated, oval, uniformly firm lymph node measuring 1.5 cm. in its longest dimension. The cut surface showed mottled, yellow-tan areas with a small hemorrhagic area.

Microscopically, sections of the myxomatous tissue removed from the defect in the skull (figure 2) showed a granulomatous reaction. The inflammatory cells were mainly histiocytes, many of which contained abundant foamy cytoplasm. There were also numerous neutrophils, plasma cells and lymphocytes. Many attempts to demonstrate or distinguish eosinophils with different stains failed. The surrounding stroma was necrotic, hemorrhagic and very hyperemic. A very small amount of fibrosis was present. A few multinucleated giant cells of the foreign body type were present.

Sections of the lymph node showed infiltration by a similar granulomatous tissue rich in large, "foamy" histiocytes. Smaller numbers of other inflammatory cells were present. Except for the infiltration with granulomatous tissue, the lymph node was not remarkable (figure 3).

Sections stained by Sudan IV to bring out the presence of fat in these large, foamy histiocytes showed these cells to contain orange-colored droplets of what was probably cholesterol.

There was no evidence whatsoever of malignancy or of specific inflammation.

Dr. George Hartley, Jr., the pathologist who examined and reported upon these sections, felt that this picture was consistent with a diagnosis of "histiocytosis X (S-C syndrome), disseminated, with early lesions of skull and cervical lymph node."

The tissue was sent for confirmation to Dr. Louis Lichtenstein,[2, 9] who agreed with this diagnosis. He remarked that the absence of constitutional symptoms was a good omen as far as prognosis was concerned, but warned that the boy should be carefully checked periodically for several years. He also suggested roentgen therapy as the treatment of choice, directed against both the skeletal and the osseous lesions.

However, by the time this communication from Dr. Lichtenstein was received the patient was responding so well to treatment that a change in therapy was considered inadvisable.

The operative wounds healed nicely, and during the period of healing 80 units of ACTH (HP) Gel were administered every other day. There was no apparent interference with wound healing, and the blood pressure, urinalyses, temperature, etc., remained normal. The patient was ambulatory within 24 hours after surgery.

Regression in the size of the remaining cervical lymph nodes was prompt, being noticeable within 48 hours after the first injection of corticotropin. The sutures were removed on the sixth postoperative day.

After the first week the dosage of ACTH Gel was reduced to 40 units three times weekly, and at the end of the third week the serum cholesterol was found to be 168 mg. per 100 c.c. of whole blood. The blood counts were normal, and the erythrocyte sedimentation rate was 14 mm. fall per hour.

All signs of lymphadenopathy had subsided. The spleen was not palpable, and the patient was hard at work, with no apparent disability. Treatment with ACTH was discontinued at the end of the first month.

Three months later further x-rays of the skull showed that the defect in the right frontal bone had decreased in size by more than 50% and its margins had become smooth. No other osteolytic lesions had appeared.

The patient continued to remain healthy, and at the end of the seventh month a third x-ray of the skull showed that the defect in the skull had been almost completely filled in except for a 2 cm. area in the outer table.

The patient remained completely well until the end of the fourteenth month, when he noticed a recurrence of the enlargement of the right posterior cervical and occipital lymph nodes. During the interim he had continued school and work, sometimes walking five miles or more per day. This new attack of painless and afebrile lymphadenopathy was characterized by a marked overgrowth of lymphoid tissue (adenoids) in the nasopharynx, and bilateral inguinal adenopathy had appeared.

His blood picture was as follows: erythrocytes, 5,050,000; leukocytes, 5,550 (with 64% normal lymphocytes, 35% neutrophils and 1% eosinophils); hemoglobin, 99% (14.3 gm.). The only abnormality was the lymphocytosis.

A second biopsy of a cervical lymph node was done on June 27, 1955. A sternal bone marrow puncture was also done. This was found to be entirely normal.

The pathologist remarked after examination of the lymph node: "If one did not know the past history of this patient, I am sure that the diagnosis of histiocytosis would not be entertained from the appearance of the above lymph node."

Section of the lymph node showed marked reticular hyperplasia, the germinal centers being extremely active and slightly enlarged. In some of the sinusoids there were large cells containing much eosinophilic cytoplasm, which possibly represented degenerated histiocytes. Eosinophilic neutrophils were conspicuous by their absence.

X-ray studies during this hospital stay showed almost complete healing of the defect in the skull. Only a faint residual rarefaction of the diploë remained (figure 1). No new cranial or other skeletal lesions were seen. The lung fields were entirely clear. The heart and great vessels were normal in size and contour, and the bones of the thorax appeared healthy.

The previously noted lymphocytosis of 64% in the peripheral blood fell to a normal 32% within 10 days after a single intramuscular injection of corticotropin. Also, the lymphadenopathy promptly subsided.

Upon being discharged from the hospital the patient was advised to watch for any further signs of enlarging or tender lymph nodes, and if they appeared, to have treatment with ACTH without delay.

Three months later he "caught cold," and came to the office with a mild fever, sore throat and earache. The same hypertrophy of adenoid tissue in the nasopharynx was again noted. He was treated with a single injection each of benzathine-penicillin-G (Bicillin), 600,000 units, and 80 units of corticotropin gel, with prompt recovery.

Again, in January, 1956, he developed an acute viral pneumonitis of the right lower lobe, and the same pharyngeal adenoid tissue again became hypertrophied. His blood count showed 48% lymphocytes and 5% eosinophils. There was no leuko-

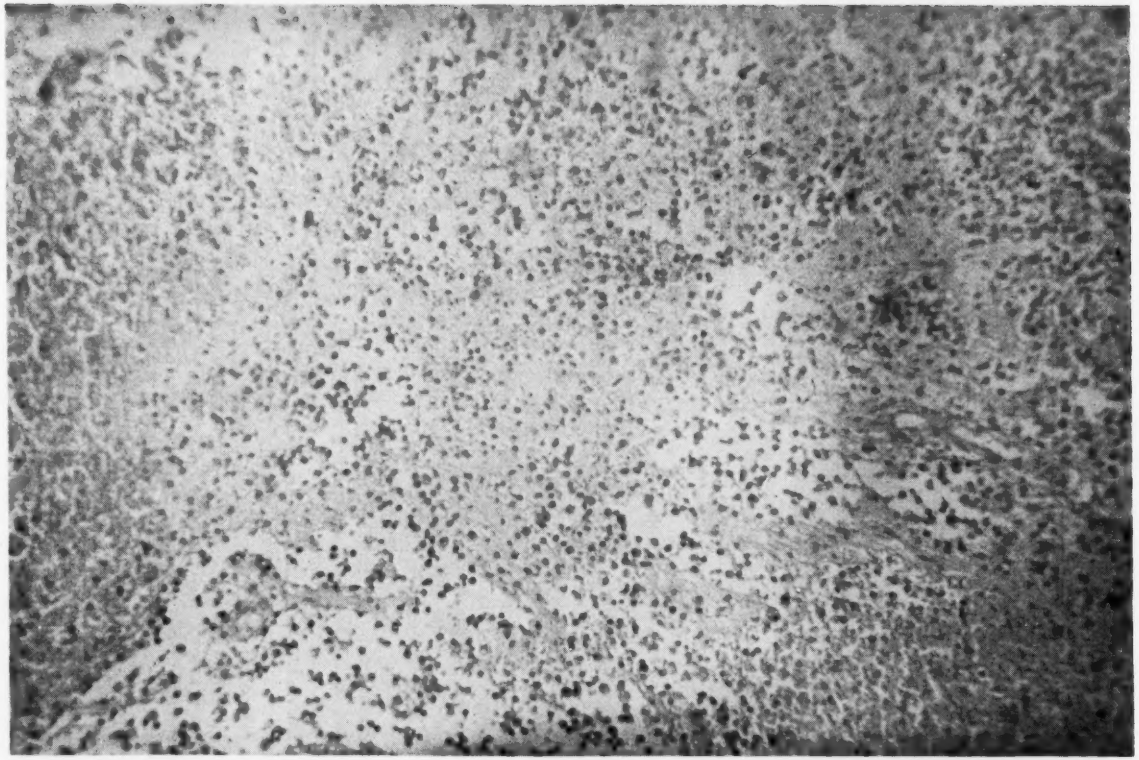

FIG. 2A. *Case 1.* Section of myxomatous tissue showing typical granulomatous reaction, removed from the defect in the skull. Low magnification: × 100. The inflammatory cells are mainly histiocytes containing abundant, foamy cytoplasm. There are also numerous neutrophils, plasma cells and lymphocytes, but no eosinophils. Very little fibrosis is present. Occasional multinucleated giant cells, of the foreign-body type, are also seen.

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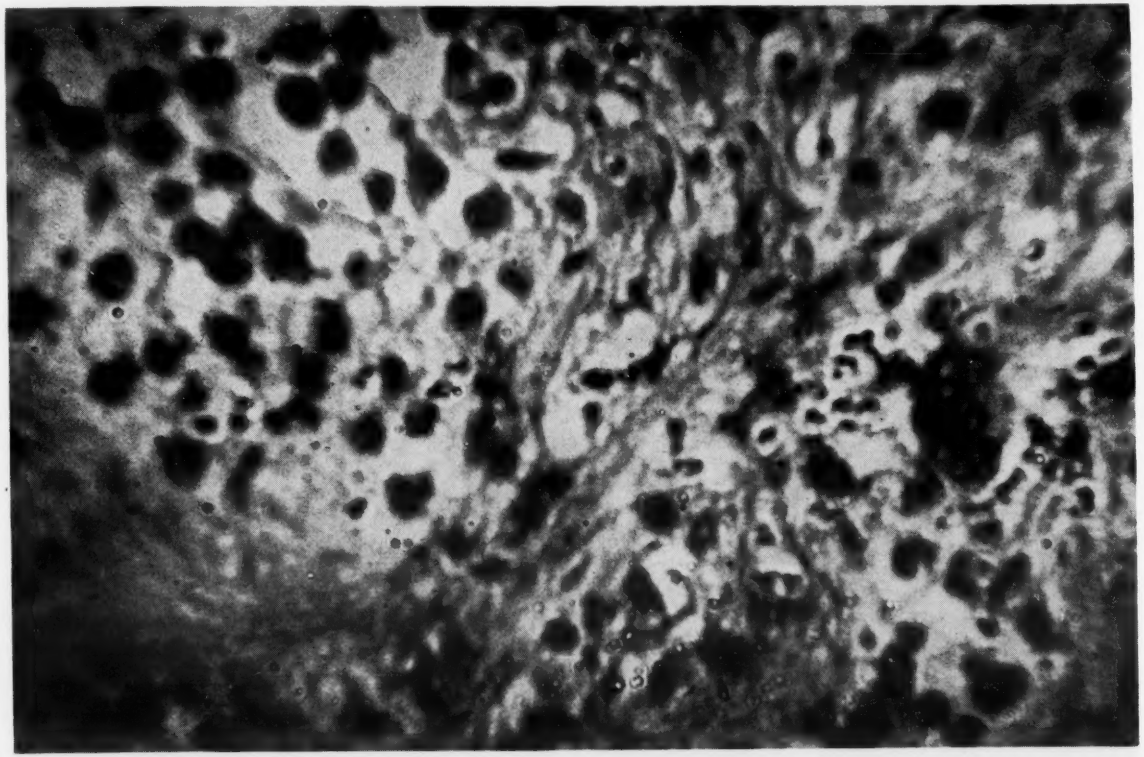

FIG. 2B. *Case 1.* Section of myxomatous tissue showing typical granulomatous reaction, removed from the defect in the skull. High magnification: × 460.

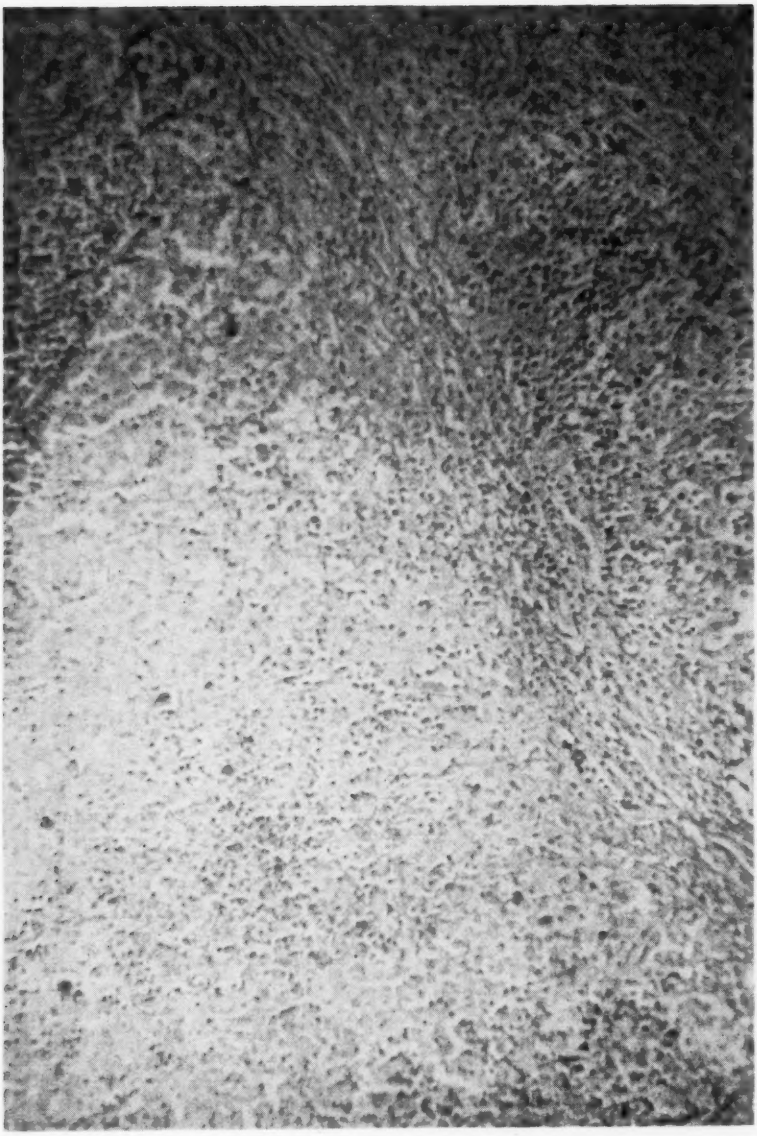

FIG. 3A. *Case 1.* Section of lymph node, showing infiltration by granulomatous tissue rich in large, foamy histiocytes, similar to those seen in the skull lesion (figure 2). Low magnification: × 100.

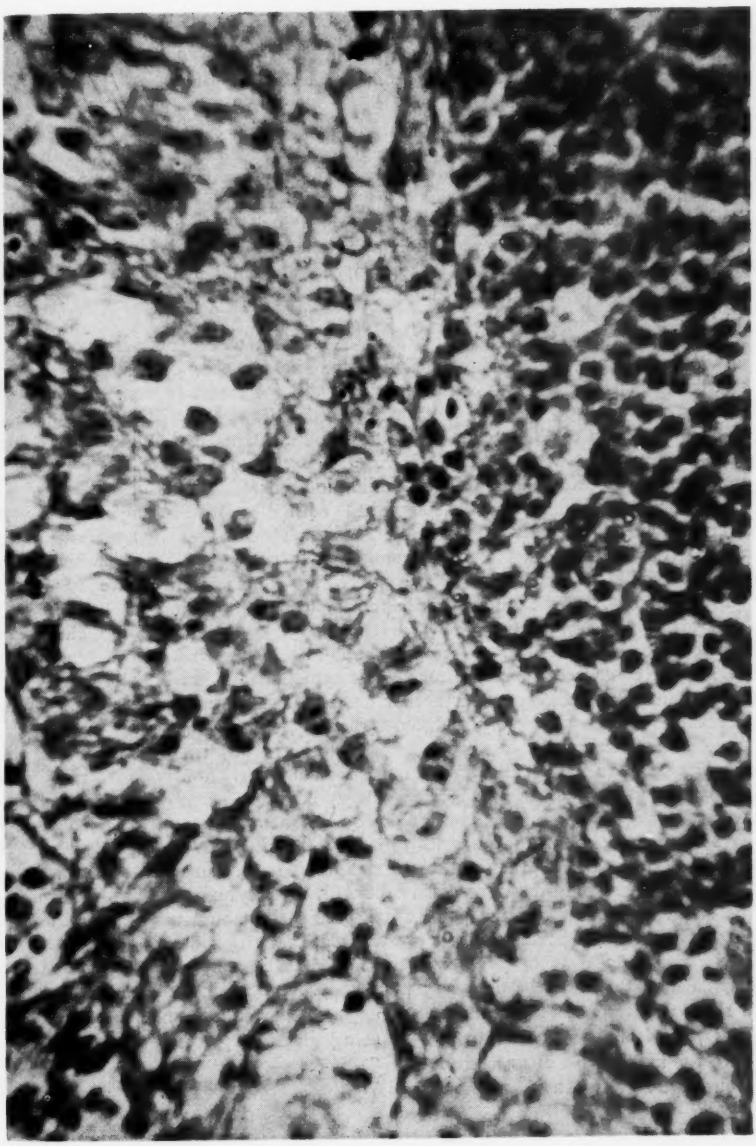

FIG. 3B. *Case 1.* Same as figure 3A. High magnification: × 460.

cytosis. The C-reactive protein test was negative. The serologic test for syphilis was negative. Urinalysis was normal. Chest x-ray showed only increased linear markings in the right base, which cleared entirely within three days following an injection of 80 units of zinc-corticotrophin and 800,000 units of procaine-penicillin-G.

Since then the patient has enlisted in the Air Force and is doing very well at a jet-training base, no recurrences having been reported.

Case 2. Our second case is that of a 24 month old white male child who developed an unusual skin rash, together with a generalized lymphadenopathy, at the age of three months. The rash was generalized, xanthomatous, patchy and maculopapular, and involved the entire body and the extremities.

The child's birth, growth and early development had been quite normal prior to the appearance of the skin lesion and the lymphadenopathy at three months. At that time the liver and spleen were found to be enlarged, and mild normochromic, normocytic anemia was found to be present, together with 56% lymphocytes and an eosinophilia of 6%.

A skin biopsy taken from the left thorax, at a point where the integument was especially rough, granular and pigmented, showed the presence of numerous histiocytes and occasional lymphocytes immediately beneath the intact superficial squamous epithelial layer. Marked edema of the corium accompanied the histiocytic infiltrate, and hyperpigmentation of the basilar cells was present. This histiologic picture was thought to be consistent with histiocytosis X (L-S syndrome).

Immediately thereafter, because of a mild, intercurrent febrile episode, an injection of procaine-penicillin-G (400,000 units) with dihydrostreptomycin, 0.5 gm., was given. Approximately two weeks later a lymph node was removed from the left inguinal region for biopsy, and a specimen of bone marrow was obtained from the left tibia. The latter was not remarkable. At the same time a second skin specimen was taken from a xanthomatous area on the right thigh.

Upon histologic examination the lymph node was found to contain clumps of reticuloendothelial cells in small rows and tongue-like projections. These cells were fairly large and contained finely granular pink cytoplasm. Their nuclei were large and darkly stained with heavy and irregular chromatin material. The normal lymph node structure was not completely replaced by these cells.

The skin sections again showed clumps and islets of reticuloendothelial cells, which, however, were not identical with those seen in the lymph nodes. They were arranged in irregular clumps just beneath the epidermis. Their most striking features were the slightly granular, eosinophilic cytoplasm and the heavily chromatized nuclei. They were similar to the cells found in the previous skin biopsy. These cells did not exhibit the characteristics of malignant cells, but it was felt that the changes seen in these biopsies were consistent with histiocytosis X (L-S syndrome).

The subsequent course of the patient has been smooth and uneventful thus far. The only treatment being administered presently is oral iron and vitamins. Growth and development appear to be proceeding normally. The skin lesions persist, as do the lymphadenopathy and the hepatosplenomegaly. Inasmuch as roentgenographic studies show no evidence of osseous or pulmonary abnormalities, no specific therapy —such as prednisolone or corticotropin—is being given at present, but will be kept in reserve for use in case of necessity.

(Courtesy, Dr. Robert W. Danielson.)

Discussion

It now seems fairly clear that the different forms of the nonlipoid reticuloendothelioses are diverse manifestations of a single disease process. The

most rapid and disseminated form (L-S syndrome) is seen most frequently in infants and young children, and is usually characterized, in its most fulminating and rapidly progressive form, by generalized lymphadenopathy, hepatosplenomegaly, anemia, purpura, cachexia and a rapidly fatal outcome. On rare occasions this acute progressive form is seen in adults. Two such cases have been reported recently by Paull and Phillips.[12] One of their adult cases clinically resembled multiple myeloma, the other resembled a malignant lymphoma. Neither of these cases responded in the slightest to the administration of antibiotics and, although one of them was given ACTH during the final six days of illness, no benefit was derived from it.

These cases again remind us of the extremely thin line of demarcation between the benign and the malignant forms of disease. This was illustrated by the case reported by Gray and Taylor,[8] to which reference has previously been made. Lesions which are localized and essentially benign histologically in their early stages may progress for no apparent reason, in spite of, or even because of, treatment; or they may spontaneously regress. However, progression from a benign to a malignant phase is by no means the usual course of this disease. The xanthomatous lesions of the skin, and the lymphadenopathy and hepatosplenomegaly, have been known to subside spontaneously, as in our second case. It seems more likely, however, that such widespread lesions would tend to progress rapidly to a fatal termination. Such an occurrence, in an elderly individual, was recently reported by Goldner and Volk.[13]

Osseous lesions, as exemplified by our first case, that of the young man, may produce very little in the way of symptoms. As a matter of fact, in the strictly localized lesions of eosinophilic granuloma, where the bone lesions are the sole manifestation of the disease, spontaneous healing has been known to occur.

When the liver, spleen and lymph nodes are enlarged, as in our second case, the anemia might be explained on the basis of hypersplenism. With involvement of the brain or its coverings, neurologic signs and symptoms might be present. If the area of the hypothalamus or its connections to the hypophysis are involved, diabetes insipidus (one of the S-C triad) might result. If the lung is involved, pulmonary signs and symptoms, such as chronic cough, dyspnea, pulmonary fibrosis and even chronic cor pulmonale, might eventually result.

Thus, as in many other diseases, the clinical picture produced by histiocytosis-X depends upon the extent of the involvement, the rapidity of the process, and the organs involved. Of course, we have no way of knowing at the present time what the final outcome of these two cases will be. We might have to wait for many years. Nevertheless, we feel that the prognosis is good, and we find solace in the fact that our first case is at the present time considered to be completely well and fit for duty in the U. S. Air Force. Furthermore, we prefer to believe that the treatment which we chose to give has a great deal to do with this apparently favorable result.

Summary

A case of chronic, disseminated reticuloendotheliosis—histiocytosis-X (S-C)—is presented. The case is considered to be especially interesting because of its prompt response to corticotropin therapy. The effect of antibiotics administered simultaneously is less clear, although they possibly contributed in some degree to the favorable outcome. A second case, in a child, of the disseminated, subacute form of the disease—histiocytosis-X (L-S), with involvement of skin, lymph nodes, liver and spleen—is also presented. Transition from the subacute (L-S) phase to the chronic (S-C) phase has been observed.

Both of these cases have been positively diagnosed by means of repeated biopsies from affected organs. These studies are fully described and illustrated, along with all other pertinent clinical data.

The recent literature has been briefly reviewed, and the terminology and classification of Lichtenstein [2] has been adopted. Under this unified concept the various nonlipoid reticuloendothelioses, including (A) eosinophilic granuloma, (B) Hand-Schüller-Christian disease, and (C) Letterer-Siwe disease, are all regarded as different forms or phases of a single nosologic entity, termed histiocytosis-X. It is felt that these two cases add further proof of the reasonableness of this unified concept.

Acknowledgment

Grateful acknowledgment is made to the following members of the staff of the hospital for their kind assistance in preparing this report:

George Hartley, Jr., M.D., pathologist
C. W. Bruner, M.D., radiologist
Robert W. Danielson, M.D., for case 2
Mr. J. C. Cullen, laboratory technician

Grateful acknowledgment is also made to Dr. Louis Lichtenstein, of the Wadsworth General Hospital, Los Angeles, for his help in case 1, and for the use of his tables 1 and 2.

Summario in Interlingua

Le litteratura medical cognosce pauco frequente reportos relative a iste benigne, inflammatori e leve granuloma invasive de non-cognoscite etiologia. Hodie illo es considerate per multos como causate per un agente infectiose e es designate como "histiocytosis X." Sub iste termino on pote classar le varie entitates clinic que es cognoscite como (a) granuloma eosinophilic de osso, (b) morbo de Hand-Schüller-Christian, e (c) morbo de Letterer-Siwe. Le relation inter iste differente morbos ha essite illustrate, e le rationes pro classar los como differente manifestationes del mesme entitate pathologic fundamental es presentate de novo. Es presentate un breve revista del recente litteratura in re iste thema, e duo recentemente observate casos es reportate. Le prime es le caso de un juvene adulto mascule con le typo chronic e disseminate del morbo, i.e. histiocytosis X (S-C). Iste patiente se presentava al consulta medical originalmente a causa de un tumescentia al latere dextere de su collo. Ille etiam habeva un area "contusionate" al fronte. Ben que su matre habeva inviate le al medico proque illa pensava que ille habeva parotitis, il esseva promptemente establite que ille habeva le mentionate typo de reticuloendotheliosis, e omne le signos e symptomas subsideva in le curso del tempore post le institution

de un therapia a corticotropina e antibioticos. Le secunde caso es illo de un puero qui habeva le plus acute e disseminate forma del morbo, i.e. histiocytosis X (L-S), con affection del pelle, del nodos lymphatic, del hepate, e del splen. Anemia, lymphocytosis, e eosinophilia esseva etiam presente, sed proque iste signos non es incommun in infantes e juveniles, illos es possibilemente sin grande o mesmo sin ulle signification. In ambe casos, repetite biopsias de organos afficite esseva effectuate, e le diagnose esseva positivemente establite in ambes. Le effecto benefic e possibilemente curative de antibioticos e corticotropina es notate.

BIBLIOGRAPHY

1. Fraser, J.: Skeletal lipoid granulomatosis (Hand-Schüller-Christian's disease), Brit. J. Surg. **22**: 800, 1953.
2. Lichtenstein, L.: Histiocytosis X, integration of eosinophilic granuloma of bone, "Letterer-Siwe disease," and Schüller-Christian disease as related manifestations of a single nosologic entity, Arch. Path. **56**: 84, 1953.
3. Bierman, H. R., Lanman, J. T., Dod, K. S., Kelly, K. H., Miller, E. R., and Shimkin, M. B.: The ameliorative effect of antibiotics on nonlipoid reticuloendotheliosis (Letterer-Siwe disease) in identical twins, J. Pediat. **40**: 269, 1952.
4. Letterer, E.: Aleukamische Retikulose, Frankfurt. Ztschr. f. Path. **30**: 377, 1924.
5. Siwe, S. A.: Die Reticuloendotheliose ein neues Krankheitsbild unter den Hepathosplenomegalien, Ztschr. f. Kinderh. **55**: 212, 1933.
6. Blahd, W. H., Levy, M. S., and Bassett, S. H.: A case of Hand-Schüller-Christian syndrome treated with cortisone, Ann. Int. Med. **35**: 927, 1951.
7. Bass, M. H., Sapin, S. O., and Hodes, H. L.: Use of cortisone and corticotropin (ACTH) in treatment of reticuloendotheliosis in children, Am. J. Dis. Child. **85**: 393, 1953.
8. Gray, J. D., and Taylor, S.: Acute systemic reticulo-endotheliosis terminating as a monocytic leukaemia, Cancer **6**: 333, 1953.
9. Lichtenstein, L., and Jaffe, H. L.: Eosinophilic granuloma of bone, with report of a case, Am. J. Path. **16**: 595, 1940.
10. May, I. A., Garfinkle, J. M., and Dugan, D. J.: Eosinophilic granuloma of lung: report of three cases, Ann. Int. Med. **40**: 549, 1954.
11. Childers, J. H., Middleton, J. W., and Schneider, M.: Eosinophilic granuloma of femur and lungs: a case report, Ann. Int. Med. **42**: 1297, 1955.
12. Paull, A. M., and Phillips, A. M.: Systemic reticuloendotheliosis (Letterer-Siwe disease) in the adult male, Ann. Int. Med. **41**: 363, 1954.
13. Goldner, M. G., and Volk, B. W.: Fulminant normocholesteremic xanthomatosis (histiocytosis X), Arch. Int. Med. **95**: 689, 1955.

CASE REPORTS

INTRAHEPATIC OBSTRUCTIVE JAUNDICE FOLLOWING THE ADMINISTRATION OF 75 MG. OF CHLORPROMAZINE*

By Edward E. Woldman, M.D., F.A.C.P., and David Fishman, M.D.,
Cleveland, Ohio

Chlorpromazine (Thorazine) is being widely used in the treatment of various psychiatric disorders,[1] the nausea and vomiting of diverse etiology,[2] intractable hiccups,[3] and as an analgesic.[4] The sedative, tranquilizing and calming properties of the drug also make it useful as an adjunct in the treatment of a variety of conditions.

Numerous side-effects have been noted following the administration of chlorpromazine, but most of them are usually not severe enough to warrant discontinuing the drug therapy. However, one of the most disturbing side-effects of this therapy is jaundice, which has been reported quite frequently during this last year. The laboratory observations made on these patients are those usually found in extrahepatic biliary obstruction and, as a result, some patients have been subjected unnecessarily to exploratory laparotomy.

The present report describes the occurrence of intrahepatic obstructive jaundice in a patient who had ingested only 75 mg. of chlorpromazine. A needle biopsy of the liver of this patient had been performed.

Case Report

A 53 year old white woman was admitted to St. Luke's Hospital on January 12, 1956, complaining of jaundice of two weeks' duration. On December 9, 1955, she had felt very nervous and had taken 25 mg. of chlorpromazine three times that day, for a total of 75 mg. She had never taken chlorpromazine prior to this date, nor had she taken any since. About two weeks later she began to complain of malaise, anorexia, nausea and occasional vomiting. She also complained of chills and intermittent, crampy midabdominal pain. A few days later a generalized pruritus developed, and she noted dark urine and light-colored stools. On December 27, 1955, she first noticed a slight jaundice which gradually became more intense. During the next week the symptoms abated but the jaundice persisted. The past history revealed only that she had had a hysterectomy for fibroid tumors, and an appendectomy in 1941. She was married and had three children.

Physical examination revealed a well nourished, well developed, icteric woman. The blood pressure was 132/80 mm. Hg. Examination of the abdomen showed a palpable, nontender, smooth liver edge, about two fingerbreadths below the right costal margin on deep inspiration. The remainder of the examination was entirely

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unrevealing. The urinalysis was normal except for the presence of bile, with no increase in urobilinogen. The stools were clay-colored, and were negative for occult blood. The blood cell counts were normal except for an increase in the number of eosinophils (8%). Blood sugar content, nonprotein nitrogen, creatinine and serologic tests were normal. Liver function tests were done on the first day after admission and were suggestive of obstructive jaundice (table 1). The total serum cholesterol was 550 mg. per 100 c.c., the alkaline phosphatase was 47.4 units (King-Armstrong), and the cephalin-flocculation test was negative in 24 and 48 hours, suggesting an obstructive jaundice. A biopsy of the liver was obtained with a Vim-Silverman needle; microscopic examination revealed the following: "The parenchymal cells of the liver show no microscopic abnormality. The portal spaces show a cellular infiltrate composed of lymphocytes and polymorphonuclear leukocytes, with a slight excess of lymphocytes, and an occasional eosinophil (figure 1). Some of the biliary canaliculi of the lobules are dilated and contain plugs of greenish-brown bile pigment (figure 2). The bile ducts within the portal spaces are not dilated." A diagnosis

TABLE 1
Laboratory Studies

	1/13/56	1/16	1/24	1/30
Icterus index	53	26	17	12
Bilirubin: mg.%				
Total	10.7	..	1.9	..
Direct	8.8	..	1.8	..
Cholesterol: mg.%				
Total	550	..	298	272
Free	299	..	72	..
Alkaline phosphatase				
King-Armstrong units	47.4	..	24.5	16.1
Cephalin flocculation				
(In 48 hrs.)	0	..	0	..
Prothrombin (Quick method)	86%	..	..	..
Serum protein: Gm.%	7.3	..	..	..
Serum albumin: Gm.%	4.4	..	..	..
A/G ratio	1.5	..	..	..
Urine: Bile	Positive	..	..	..
Urobilinogen	0	..	..	..
Blood eosinophils	8%	..	6%	4%

of intrahepatic obstructive jaundice was made. Cholecystography disclosed excellent filling of the gall-bladder, without evidence of calculi. Roentgenographic studies of the esophagus, stomach and duodenum were normal. The patient was placed on a high-protein diet with vitamin supplements. Her condition gradually improved and on February 1, 1956, she was completely asymptomatic and was discharged.

COMMENT

Although the occurrence of jaundice during chlorpromazine therapy has been observed by many others,[5, 6, 7] it is worthy of note that this patient ingested a total dose of only 75 mg. of chlorpromazine about two weeks prior to the onset of jaundice, and that she had not taken this drug before or after this date. There was no concurrent exposure of this patient to other hepatotoxic or icterogenic agents. The only other report in the literature of a case of chlorpromazine jaundice following a small dose of the drug was the case reported by Sussman and Sumner.[8] In their case the jaundice developed two weeks after the administration of only 50 mg. of chlorpromazine. However, no liver biopsy was obtained.

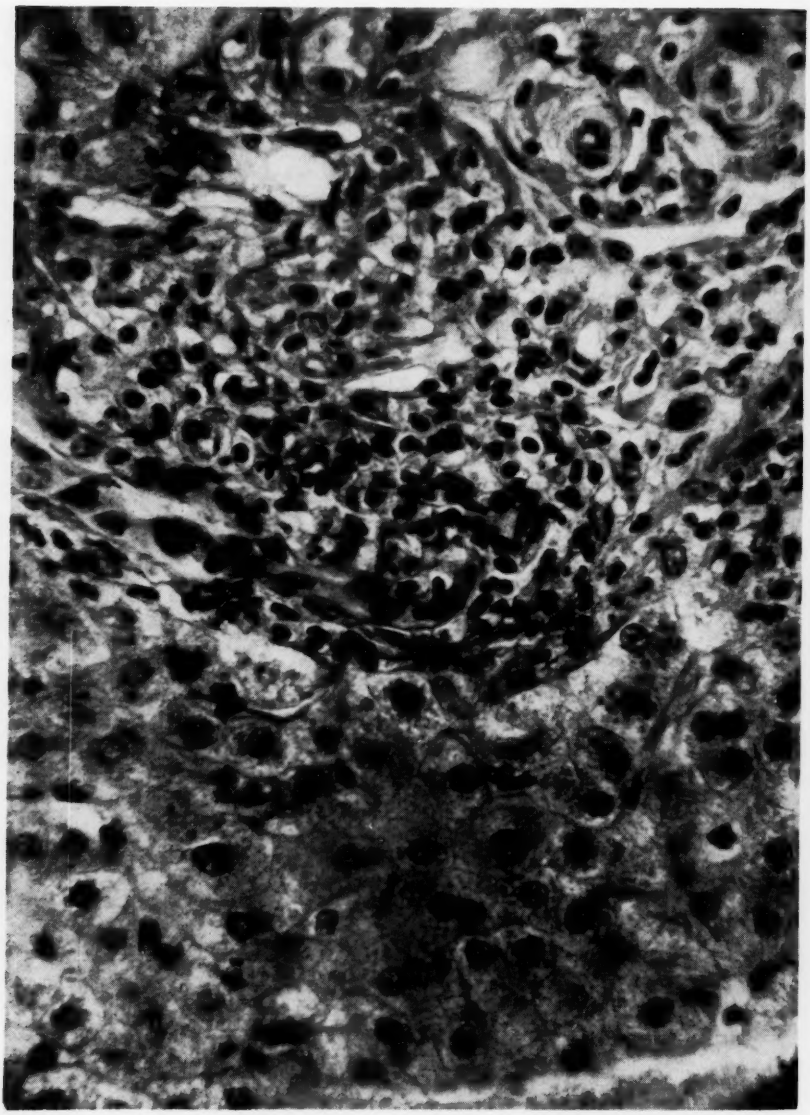

FIG. 1. Liver biopsy showing infiltration of the portal area by neutrophils, lymphocytes and few eosinophils. The hepatic cells are normal. (× 400.)

It is interesting to note that our patient had a 26 year old daughter who was being treated by a psychiatrist with chlorpromazine in doses of 100 mg. daily for a period of three months, or a total of approximately 9,000 mg. The daughter showed no evidence of jaundice, yet the mother, who took only 75 mg. of the

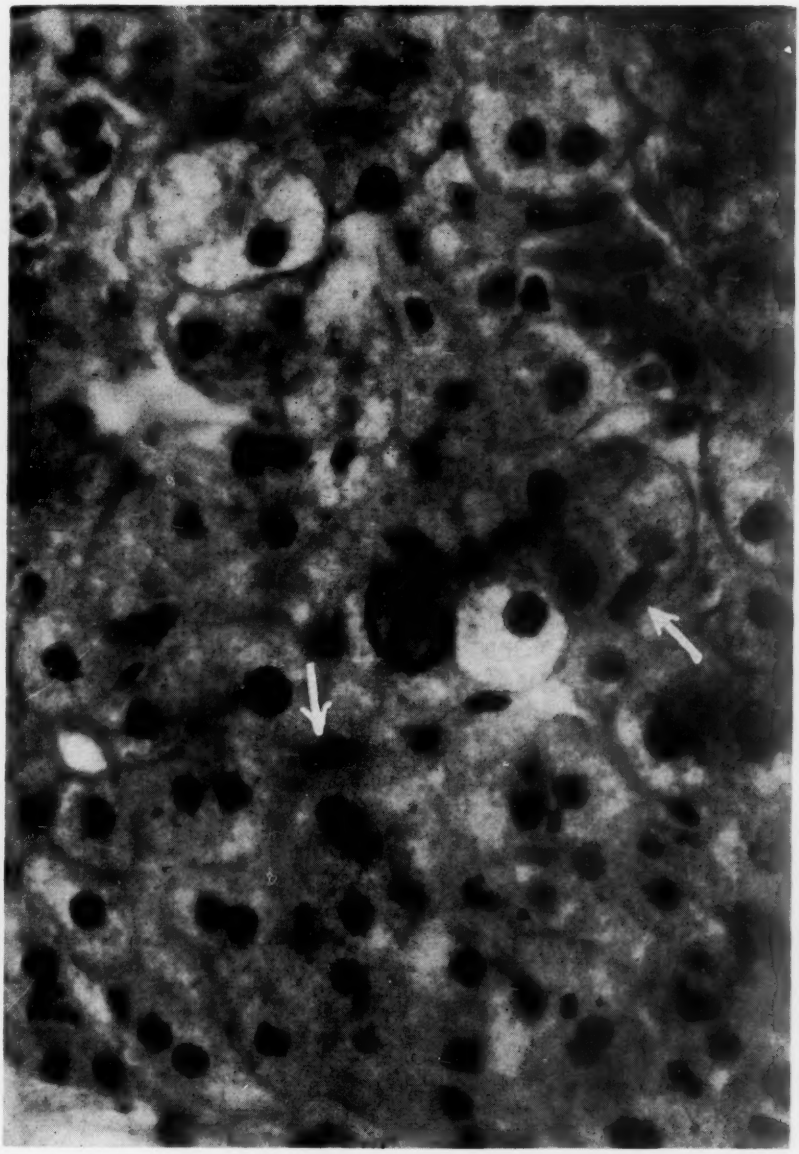

FIG. 2. Liver biopsy showing bile stasis as indicated by the bile thrombi in the small biliary radicles. (× 900.)

same drug, developed severe jaundice two weeks later. Chlorpromazine jaundice is very rare in the young individual. Most of the cases reported in the literature were past the age of 40.

Apparently the amount of the drug does not influence the severity of the disease. In our case the jaundice was more severe after the administration of only 75 mg. of the drug than in many cases reported in the literature who had ingested larger doses of chlorpromazine for a longer period of time. The reaction depends upon the individual's sensitivity to the drug, rather than upon the total amount taken.

Cohen and Archer [9] have concluded that chlorpromazine is not hepatotoxic even after prolonged administration, and they believe that jaundice is the result of individual idiosyncrasy to the drug. An elevated eosinophil count in the peripheral blood occurs in such cases, and the association of cholestatic jaundice with eosinophilia [10, 11] emphasizes the effect of hypersensitivity in the pathogenesis of chlorpromazine jaundice. This variety of icterus has features similar to those described as occurring after administration of methyl testosterone,[12] thiouracil [13] and arsphenamine.[14] As in chlorpromazine jaundice, the results of laboratory examination in these instances indicated obstructive jaundice with little or no parenchymal injury.

Our case showed a typical picture of intrahepatic obstructive jaundice. The test for hepatocellular damage was negative, while the serum cholesterol and the alkaline phosphatase were markedly elevated. The urine showed the presence of bile and an absence of urobilinogen. There was a transient eosinophilia in the peripheral blood. The liver biopsy showed preservation of the parenchymal cells. The portal areas were infiltrated with neutrophils, lymphocytes and a few eosinophils. The biliary radicles were not dilated, and there were bile plugs in the biliary canaliculi. The cholecystograms were normal.

It is difficult to differentiate intrahepatic obstructive jaundice due to chlorpromazine from extrahepatic obstructive jaundice resulting from such conditions as carcinoma of the pancreas or common duct stone. Recognition of this syndrome is important in order to prevent unnecessary surgery. A history of chlorpromazine therapy and the laboratory finding of a transient eosinophilia are important aids in differentiating between the two types of jaundice. A liver biopsy should be done on all doubtful cases so that unnecessary laparotomy can be avoided.

It is important to note that the icterus may develop some time after the administration of the drug has been discontinued. Chlorpromazine jaundice has been reported as a delayed phenomenon, usually occurring after the second week of its administration. Since the development of jaundice depends upon the individual's sensitivity to chlorpromazine, rather than upon the total amount taken, and since the icterus usually develops after the second week of its administration, it may be advisable to administer the drug for one or two days and then wait for a period of about two weeks to determine whether the individual is sensitive to chlorpromazine before continuing the drug.

Summary and Conclusions

A case is described of intrahepatic obstructive jaundice developing two weeks after the ingestion of only 75 mg. of chlorpromazine. Hyperbilirubinemia and

marked elevation of the alkaline phosphatase and total cholesterol, with a negative cephalin flocculation test, characterized the chemical investigation. The peripheral blood showed a transient eosinophilia. A biopsy of the liver was performed.

The relation between drug ingestion and the appearance of jaundice is suggestive of hypersensitivity, and the reaction depends upon the individual's sensitivity to the drug rather than upon the total amount taken. It is suggested that physicians who prescribe the use of chlorpromazine should administer this drug for one or two days and then wait two weeks to determine whether a hypersensitivity to this drug is present.

Summario in Interlingua

Es describite un caso de jalnessa obstructive intrahepatic que se disveloppava duo septimanas post le ingestion de solmente 75 mg de chlorpromazina. Ben que le occurrentia de jalnessa durante therapias a chlorpromazina ha essite observate per multe alteros, le sol previe reporto publicate de un caso de jalnessa post un parve dose del droga es illo de Sussman e Sumner (in *New England J. Med.* **253**: 499, 1955).

Le patiente del presente reporto esseva un femina blanc de 53 annos de etate qui habeva prendite in le curso de un die un total de 75 mg de chlorpromazina in tres doses de 25 mg. Illa habeva nunquam prendite chlorpromazina ante le episodio hic reportate, e non ha prendite ullo depost. Le patiente non esseva concurrentemente exponite a altere agentes hepatotoxic o icterogene. Circa duo septimanas post le ingestion de chlorpromazina, illa se plangeva de malaise, anorexia, nausea, e vomito sporadic. Alicun dies plus tarde illa notava urina de color obscur, feces de color clar, e leve grados de jalnessa que gradualmente deveniva plus intense.

Le examine del abdomine monstrava solmente un palpabile, non-sensibile, e lisie margine hepatic que se notava in respiration profunde a duo largores de digito infra le margine dextero-costal. Le tests del function hepatic indicava jalnessa obstructive. Le cholesterol total del sero esseva 550 mg pro 100 cm^3. Le phosphatase alcalin esseva 47,4 unitates (King-Armstrong). Le test de flocculation a cephalina esseva negative a 24 e 48 horas. Le numerationes del cellulas sanguinee esseva normal, a parte un augmento del numero de eosinophilos (8%).

Un biopsia del hepate revelava le sequente factos: Le cellulas parenchymal del hepate monstrava nulle anormalitate microscopic. Le spatios portal monstrava un infiltrato cellular componite de lymphocytos e leucocytos polymorphonuclear, con un leve excesso de lymphocytos e sporadic eosinophilos. Alicunes del canaliculos biliari del lobulos esseva dilatate e contineva tampones de pigmento biliari de color verdastre brun. Le ductos biliari intra le spatios portal non esseva dilatate. Esseva formulate un diagnose de jalnessa obstructive intrahepatic. Cholecystographia revelava excellente plenation del vesica biliari sin evidentia de calculos. Le condition del patiente se meliorava lentemente. Quatro septimanas plus tarde, illa esseva completemente asymptomatic e poteva esser dimittite.

Es importante notar que le ictero pote disveloppar se un certe periodo de tempore post que le administration del droga ha essite interrumpite. Jalnessa a chlorpromazina ha essite reportate como phenomeno retardate, occurrente usualmente post le secunde septimana del administration del droga. Proque le disveloppamento del jalnessa depende del sensibilitate del individuo a chlorpromazina plus tosto que del quantitate total del droga ingerite e proque le ictero se disveloppa usualmente post le secunde septimana del administration de illo, il es forsan a recommendar administrar le droga un o duo dies e attender postea un periodo de circa duo septimanas pro determinar si o non le individuo in question es sensibile a chlorpromazina.

BIBLIOGRAPHY

1. Lehmann, H. E., and Hanrahan, G. E.: Chlorpromazine: a new inhibiting agent for psychomotor excitement and manic states, Arch. Neurol. and Psychiat. **71**: 227–237 (Feb.) 1954.
2. Friend, D. G., and Cummins, J. F.: New antiemetic drug: preliminary report, J. A. M. A. **153**: 480 (Oct. 3) 1953.
3. Friedgood, C. E., and Ripstein, C. B.: Chlorpromazine (Thorazine) in treatment of intractable hiccups, J. A. M. A. **157**: 309 (Jan. 22) 1955.
4. Sadove, M. S., Levin, M. J., Rose, R. F., Schwartz, L., and Witt, F. W.: Chlorpromazine and narcotics in the management of pain of malignant lesions, J. A. M. A. **155**: 626–628 (June 12) 1954.
5. Lemire, R. E., and Mitchell, R. A.: Regurgitation type jaundice associated with chlorpromazine (Thorazine) administration, J. Lab. and Clin. Med. **44**: 285 (Nov.) 1954.
6. Zatuchni, J., and Miller, G.: Jaundice during chlorpromazine therapy, New England J. Med. **251**: 1003–1006 (Dec. 16) 1954.
7. Boardman, R. H.: Fatal case of toxic hepatitis implicating chlorpromazine, Brit. M. J. **2**: 579 (Sept. 4) 1954.
8. Sussman, R. M., and Sumner, P.: Jaundice following the administration of 50 mg. of chlorpromazine, New England J. Med. **253**: 499–502 (Sept. 22) 1955.
9. Cohen, I. M., and Archer, J. D.: Liver function and hepatic complications in patients receiving chlorpromazine, J. A. M. A. **159**: 99–101 (Sept. 10) 1955.
10. Van Ommen, R. A., and Brown, C. H.: Obstructive-type jaundice due to chlorpromazine (Thorazine), J. A. M. A. **157**: 321–325 (Jan. 22) 1955.
11. Harnett, B. S.: Liver damage and eosinophilia following chlorpromazine therapy: report of a case, Brit. M. J. **1**: 1458 (June 18) 1955.
12. Werner, S. C., Hanger, F. M., and Kritzler, R. A.: Jaundice during methyl testosterone therapy, Am. J. Med. **8**: 325–331 (Mar.) 1950.
13. Gargill, S. L., and Lesses, M. F.: Toxic reactions to thiouracil: report of cases with one fatality, J. A. M. A. **127**: 890–898 (Apr. 7) 1945.
14. Hanger, F. M., Jr., and Gutman, A. B.: Postarsphenamine jaundice, apparently due to obstruction of intrahepatic biliary tract, J. A. M. A. **115**: 263–271 (July 27) 1940.

PROBABLE DEFICIENCY OF VITAMIN B_{12} WITH "PERNICIOUS ANEMIA" IN TWO PATIENTS WITH NORMAL SCHILLING TEST*

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PERNICIOUS anemia is due to the absence of intrinsic factor in the patient's gastric secretions, leading to an inability to absorb vitamin B_{12} present in the diet.[1] We have recently observed two patients in whom all of the classic criteria for severe pernicious anemia were present, but in whom a normal ability to absorb vitamin B_{12} from the gastrointestinal tract was demonstrated by means of the absorption test employing cobalt^{60}-labeled vitamin B_{12}.[2]

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Both patients demonstrated the following symptoms and signs: glossitis, diarrhea, vomiting, mental disturbances, generalized progressive weakness, severe macrocytic anemia, thrombocytopenia, moderate leukopenia with hypersegmented polymorphonuclear leukocytes, a megaloblastic bone marrow, hyperbilirubinemia, and achlorhydria after histamine. All of these cleared completely after treatment with vitamin B_{12} parenterally, and have not recurred in a period of five months.

We are reporting these cases because they conform to typical pernicious anemia in every respect except that the patients were able to absorb vitamin B_{12}. We have been unable to find any other recorded instance in which such a situation has been described.

Case Reports

Case 1. A 49 year old bachelor was admitted to the Veterans Administration Hospital on January 9, 1956. For about four weeks he had complained of generalized

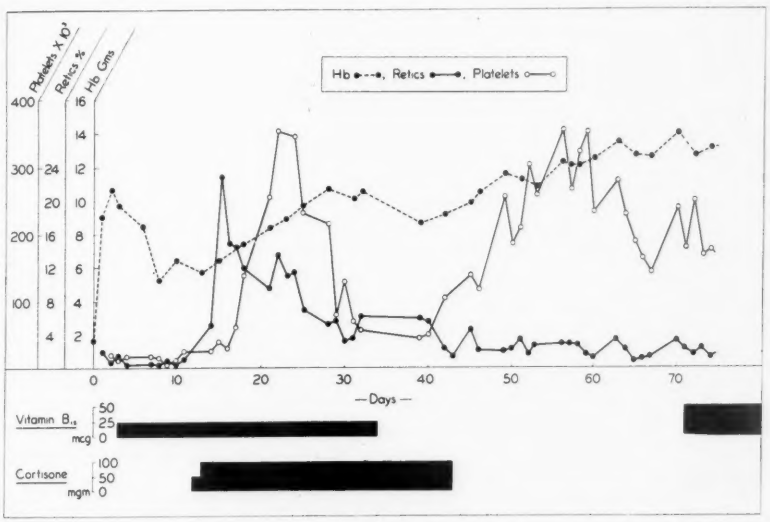

Fig. 1. *Case 1.*

weakness, dizziness, nausea and vomiting, diarrhea, occasional epistaxis and rectal bleeding, and severe thirst.

He had been in World War II, during which he had sustained an injury to the left side of his head. This was treated surgically in 1942 when a metallic plate was placed over the bony defect, but he remained greatly handicapped by persistent right-sided weakness. He had led a bed-to-wheelchair existence until one month prior to admission, when he became bedridden. Shortly thereafter he was found on the floor by his sister "in coma, bleeding slightly from the nose, and about ready to die." As soon as his mouth was cleared of food he rallied, but remained weak.

During the next three weeks he became dizzy whenever he sat up, complained of generalized weakness and malaise, was anorexic and nauseated, vomited a bilious material frequently, had frequent diarrhea, and constantly asked for water to quench

his thirst. In the week prior to admission his urine became dark yellow, and some swelling of his ankles was observed.

He had regularly consumed two to three quarts of beer and a quart of wine daily for many years. Although his appetite was poor, there had been no known loss of weight, which weight remained around 150 pounds.

At the time of admission he was deathly pale, severely confused and disoriented. He responded to questions slowly and appeared to be in cardiovascular distress. Temperature, 98.6° F.; pulse, 104; respirations, 24; blood pressure, 80/0 mm. of Hg. There was a healed scar over the left occipitoparietal area. His conjunctivae were pale and his sclerae lemon yellow. His pupils reacted sluggishly to accommodation. A gray light reflex was seen from the right pupil. In the left fundus the retina was pale and studded with flame-like hemorrhages and exudates. His lips were pale and crusted. There was acetone on his breath. His teeth were carious and caked with sordes. His tongue was without papillae and was sore. The pharynx was partially covered with a greenish yellow exudate. A tender liver edge was felt one and one-half to two fingerbreadths below the right costal margin at the end of deep inspiration. The prepuce could not be retracted over the glans penis. His extremities were thin and pale. There was resistance to passive motion of the right forearm. Weakness of the right arm and leg was most pronounced. Two to 3 plus pitting edema of the feet and ankles was present. The deep tendon reflexes were hyperactive on the right side, and clonus of the right foot and a plantar extensor response were demonstrated. There were numerous ecchymoses and petechiae, and nosebleeds were frequent.

The hematologic data are shown graphically in figure 1. The initial hemoglobin level was 1.8 gm. per 100 c.c.; hematocrit, 7%; red blood cells, 540,000 per cubic millimeter; platelet count, 8,000 per cubic millimeter. The reticulocytes were 1.1% and 0.8% on two occasions. The stained blood smear was typical of pernicious anemia: there were macrocytosis, anisocytosis, polychromatophilia, nucleated red cells, multilobed polymorphonuclear leukocytes. The low platelet count was confirmed. The total white count was 8,200, with 89% polymorphonuclears, 8% lymphocytes and 2% nonsegmented neutrophils. There were three nucleated red blood cells per 100 white blood cells.

Other pertinent laboratory data during his hospitalization were as follows:

X-ray examinations of chest, esophagus and upper and lower gastrointestinal tract revealed no diagnostic abnormalities.

January 11, 1956: Bone marrow revealed a hypercellular megaloblastic marrow. Megakaryocytes were present in adequate numbers. White blood cell count was 3,000. Occult blood was present in the stools.

January 12, 1956: Bromsulfalein retention, 22%; prothrombin activity, 60%; bilirubin: total, 20.2; direct, 10.1; indirect, 10.1; electrocardiogram, within normal limits. Platelets, 8,000. Fasting blood sugar, 85.

January 13, 1956: Occult blood in the stools; achlorhydria after histamine. White blood cell count, 15,100.

January 17, 1956: Cholesterol, total, 58; esters, 31%; cephalin flocculation, 3 plus in 24 and 48 hours.

January 23, 1956: White blood cell count, 25,000.

January 25, 1956: White blood cell count, 15,700.

January 26, 1956: Bilirubin: total, 2.8 mg.%; direct, 1.3 mg.%; indirect, 1.5 mg.%.

January 30, 1956: White blood cell count, 9,200.

January 31, 1956: Bilirubin: total, 2.0 mg.%; direct, 0.9 mg.%; indirect, 1.1 mg.%.

February 3, 1956: Bromsulfalein retention, 4.5%; cold agglutinins, negative; Coombs' test, negative, direct and indirect.

February 6, 1956: White blood cell count, 10,100.

February 13, 1956: Liver biopsy: hemosiderosis.

February 13, 1956: Bone marrow was consistent with the diagnosis of treated pernicious anemia. There was extreme hypercellularity, with both granulocytic and erythropoietic hyperplasia. Megakaryocytes were present. There was an increase in erythroblasts and normoblasts, but megaloblasts were not present at this time.

March 2, 1956: Repeated examination of the bone marrow revealed a moderate hyperplasia but no other abnormalities.

The patient was given 1,000 c.c. of whole blood the day of admission, and 1,500 c.c. the following day. Vitamin B_{12}, 25 μg per day, was started the second hospital day. The patient's mental status and appearance improved dramatically within a few days, but by the tenth hospital day there had been no reticulocytosis, and the platelets were still below 10,000 per cubic millimeter, although the white cell count had risen and the mental status improved. Profuse foul liquid diarrhea persisted during the first 10 days of hospitalization. The diagnosis of pernicious anemia was not believed to be the correct one at this time. Therefore, 100 mg. of ACTH were administered daily for the ensuing 26 days. Within one day the platelets and reticulocytes began to rise. Reticulocytes were 23% on the fifteenth day. The platelet count fell to 50,000 on the fortieth hospital day, and rose again by the fiftieth day. Throughout this period the patient continued to improve in strength and appearance. The ecchymoses and bleeding tendency disappeared by the fourteenth day, and the tongue was no longer smooth or sore.

On the eighty-sixth day a vitamin B_{12} absorption test was performed. The patient was given by mouth 0.4 μg of vitamin B_{12} labeled with about 0.4 μc of Co^{60} in 100 ml. of distilled water. Two hours later he received 1,000 μg of vitamin B_{12} parenterally. The 24-hour urine contained 15.8% of the oral dose, well within the range found in normal men.[3] This test was repeated 21 days later, using a dose of 0.3 μg of $B_{12}Co^{60}$, and the patient excreted 23.5% of the oral dose in 24 hours.

Five months later the patient continued to feel well except for his original disability due to the head injury.

Case 2. A 57 year old Negro male was admitted to the Veterans Administration Hospital on two separate occasions with multiple complaints.

The first admission was on April 15, 1955, when he complained of generalized weakness, "gas" on his stomach, difficulty with his bowels, bright red blood in his stools, and nocturia twice nightly. He had been a cook in the Army and had had a gastroenterostomy performed in 1926. The history was vague.

The patient was described as senile and markedly debilitated. Temperature, 99.4° F.; pulse, 92; respirations, 20; blood pressure, 100/60 mm. of Hg. His left pupil was smaller than the right and reacted sluggishly to light and accommodation. The few teeth remaining in his mouth were carious. There were pigmented spots on his tongue. His heart and lungs were within normal limits. There was a healed paramedian scar over his abdomen and fullness in the right upper quadrant. On rectal examination a large hard nodule was felt in the right anterolateral wall of the rectum. A similar but smaller nodule was felt on the left posteriorly. There were several hyperpigmented nodules over his sternum, left costal margin, and right external malleolus.

Laboratory Data on the First Admission:

X-rays—Chest. Emphysema and a questionable aneurysmal dilatation of the ascending aorta were reported. The aortic arch and descending aorta were tortuous and calcified.

Gastrointestinal Series. A gastroenterostomy was visualized, together with a large filling defect of the gastric antrum. An annular fungating carcinoma was sug-

gested, and a fistulous tract high on the lesser curvature aspect of the stomach was described.

Spine. Degeneration of the lumbar spine, spondylolisthesis of L_5–S_1, and calcification of the abdominal aorta were seen. Hepatomegaly was also demonstrated.

Hemoglobin, 10 gm.%; hematocrit, 34%; white blood cell count, 8,400 per cubic millimeter; acid phosphatase, 0.4 unit; alkaline phosphatase, 8.4 units; VDRL and Kolmer's test, positive (quantitative, 1:8); cerebrospinal fluid—Kolmer, negative; colloidal gold, 0111000000; protein, 19 mg.%; gastric analysis, no free acid after histamine.

An exploratory laparotomy was performed. Scarring and induration of the duodenal cap and pylorus were seen, as well as a rectal shelf of fibrous tissue. No malignancy was found at operation or histologically. The patient received penicillin because of his positive serologic reaction and was discharged improved.

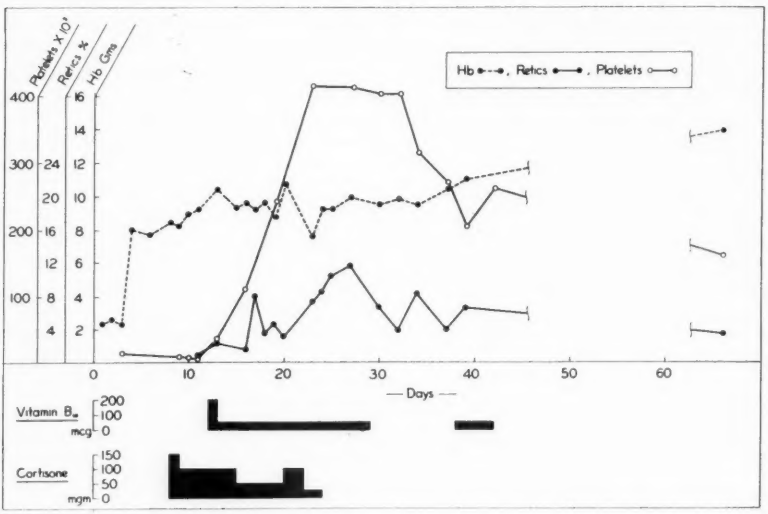

FIG. 2. *Case 2.*

The second admission was on March 4, 1956, at which time he complained of "vomiting" and "hot diarrhea." He was dehydrated, confused and semistuporous. He had chills and demonstrable muscular twitchings. Temperature, 101° F.; pulse, 100; respirations, 24; blood pressure, 90/44 mm. of Hg. His conjunctivae and oral mucous membranes were pale. His teeth were in poor repair. His tongue was dry, shiny and smooth, and there was thought to be a monilial infection of the tongue and mouth. He was breathing rapidly and shallowly. He had bloody diarrhea, nausea and vomiting. Fine râles were scattered throughout both lung fields. There were numerous ecchymoses of severe degree, and nose bleeds were frequent.

Hematologic data are shown in figure 2. At the time of admission the hemoglobin was 2.6 gm. per 100 c.c., platelets, 12,000 per cubic millimeter; reticulocytes, less than 1%; white blood cell count, 7,300. The diagnosis of pernicious anemia was not entertained because of the severe thrombocytopenia, but the peripheral smear had been described as containing multilobed polymorphonuclear leukocytes, macrocytosis,

9 nucleated red cells per 100 white blood cells, anisocytosis and polychromatophilia. The low platelet count was confirmed. Other laboratory data were as follows:

March 6, 1956: Sternal marrow on aspiration was hypercellular, and when reviewed later (March 15, 1956), was found to be consistent with the diagnosis of pernicious anemia. There was definite megaloblastosis, slightly obscured by a shift to the left in the granulocytic series. Megakaryocytes were present in adequate numbers.

March 6, 1956: White blood cell count, 7,300, with 74% polymorphonuclears, 23% lymphocytes, 3 nonsegmented neutrophils and 9 nucleated red blood cells per 100 white blood cells. Bilirubin, 2.2; direct, 1.0; indirect, 1.2.

March 12, 1956: Bilirubin, 2.0; direct, 0.9; indirect, 1.1. Reticulocytes, 0.4; platelets, 10,000.

March 15, 1956: Sternal marrow aspiration was repeated. The megaloblasts were replaced by erythroblasts, but there was no other significant change.

March 28, 1956: Repeat gastric analysis, no free acid after histamine.

Seven thousand cubic centimeters of whole blood were given in the first 11 days. The patient was given ACTH, 25 mg., on the sixth, seventh, tenth and eleventh days, and cortisone, either 100 or 50 mg., daily for 16 days beginning on the eighth day.

On the twelfth day (March 15, 1956), the case was reviewed and the diagnosis of pernicious anemia suggested. At this time, in spite of transfusions leading to a hemoglobin level of about 10 gm. per 100 c.c., the patient was still critically ill. Severe gastrointestinal bleeding was frequent, nosebleeds and occasional hematuria were present, and there were numerous large ecchymoses and generalized petechiae. The patient continued to be semistuporous. Vitamin B_{12} was given parenterally in a dose of 200 μg, and 50 μg per day were given thereafter. Within two days platelets and reticulocytes began to rise, and the mental and physical condition of the patient improved dramatically. Platelets reached 410,000 on the twenty-third day, reticulocytes 12% on the twenty-seventh day. The patient's tongue became normal in appearance, his gastrointestinal symptoms disappeared, and he felt completely well.

On the thirty-third hospital day a vitamin B_{12} absorption test was performed. The patient was given 0.4 μg of vitamin B_{12} containing about 0.4 μc. of Co^{60}. He excreted 8% of the oral dose in the 24-hour urine. The test was repeated five weeks later and 15.6% was excreted. These figures are within the range found in normal men.

Discussion

It is impossible to state with absolute assurance that the two cases described herein represent a deficiency of vitamin B_{12}. The use of cortisone and ACTH, either before or with vitamin B_{12}, spoils the neatness of a cause-and-effect relationship. In addition, transfusions were given, and this has been known to give temporary and incomplete relief in pernicious anemia.[4, 7] Determination of the serum vitamin B_{12} levels would also have been of real value, but this was overlooked in the heat of the moment. The delayed reticulocyte response in case 1 must also be explained.

Nevertheless, the evidence is overwhelming that each of these patients had a deficiency of vitamin B_{12}, leading to manifestations identical with severe pernicious anemia.

Case 1 had been an alcoholic for many years, with a poor dietary intake. The extremely high bilirubin, the abnormal cephalin flocculation and the high bromsulfalein retention are evidence in favor of liver disease. This, in combination with other dietary deficiencies, could, we believe, explain the delayed reticulocyte

response. Infection is also known to cause such a delay, and there was some evidence of respiratory infection in this patient. In spite of the lack of objective response during the first 10 days, there was definite improvement in the patient's mental status.

Case 2 was inclined to a poor diet and was known to consume large amounts of alcohol. In addition, he had a long history of gastric disturbances, and had had a gastroenterostomy for 30 years. The response elicited by vitamin B_{12} seems clear and decisive in this case. Within one to two days a dramatic change in the appearance and behavior of the patient and in the laboratory data had occurred.

The presence of thrombocytopenia and bleeding tendency served to confuse the diagnosis in these patients, although it has been previously described in severe pernicious anemia by Nittis [5] and others. We have observed four other patients with pernicious anemia in whom the diagnosis was initially obscured by the presence of thrombocytopenia.[6]

The effects of transfusion in untreated pernicious anemia have been described by Davidson [4] and Mason.[7] Both state that the effects are, in general, as follows: (a) the marrow may shift from megaloblastic to or toward erythroblastic; (b) reticulocytes are reduced further in number; (c) platelets, white cells and general condition of the patient are not improved; (d) the reticulocyte response to specific therapy is greatly reduced. Davidson described five cases who received transfusions and who then received parenteral liver therapy. The reticulocyte response to parenteral liver was reduced as a result of the transfusions; two patients transfused until their red cell counts were about 3 million per cubic millimeter had reticulocyte peaks of 10.8 and 4.0%. Three patients who were transfused to levels of about 5 million red blood cells per cubic millimeter had reticulocyte peaks of 2.4, 1.2 and 0.4%. In Mason's group of three patients the red blood cell/reticulocyte ratios were 4.3 by 10^6/1.2%, 4.9 by 10^3/2% and 4.2 by 10^3/0.5% after therapy with parenteral vitamin B_{12}.

Our case 1 responded with 22.6% reticulocytes when he had a hematocrit of 24 (estimated red blood cells, 2.5 million); and case 2 had a reticulocyte response of 11.6% after having been transfused to a hematocrit of 34 (estimated red blood cells, $>$ 3.0 million). Thus, the transfusions in these two cases did not depress the reticulocyte response to the same degree as in those reported by Davidson or Mason, but there is evidence that our patients were in more severe relapse than any they described.

The effects of ACTH in two patients with untreated pernicious anemia have been described by Wintrobe et al.[8] There was a slight, gradual, suboptimal, steplike rise in reticulocytes, no rise in platelets, no change in the marrow, no improvement in symptoms, and a subsequent satisfactory response to vitamin B_{12}. These patients were in severe relapse, with hematocrits of 11 and 19%.

It is apparent that ACTH cannot be held responsible for the effects seen in our patients, and it is reasonable to assume that cortisone could be similarly regarded. Even if one discounts the reticulocyte response, which was too definite to overlook, then the response of platelets and leukocytes, reduction in diarrhea, correction of smooth sore tongue and improvement of mental status all remain as evidence that vitamin B_{12} was effective in our patients.

Case 1 exhibited a rise in platelet count to high levels, which then fell to a rather low level, returned to a high peak, and then stabilized at normal figures

on a cycle of from about 16 to 20 days. This suggests a life span of approximately 16 to 20 days, expressed by "bursts" of platelet production.

Both of our patients, each of whom had achlorhydria, would have been called cases of pernicious anemia prior to the availability of the vitamin B_{12} absorption test. The fact that both patients were shown to be capable of absorbing vitamin B_{12} from the gastrointestinal tract makes it necessary to list them as cases of "probable deficiency of vitamin B_{12}," leading to manifestations identical with those of pernicious anemia.

Summary

Two patients are described in whom there were clinical and hematologic manifestations typical of pernicious anemia in relapse. Both patients had a long history of poor dietary intake, and each was capable of absorbing vitamin B_{12} from his gastrointestinal tract.

Addendum

Since this paper was submitted for publication, another paper has been published which contains careful documentation of vitamin B_{12} deficiency by means of serum vitamin B_{12} levels as well as other studies (Polycove, M., Apt, L., and Colbert, M. J.: Pernicious anemia due to dietary deficiency of vitamin B_{12}, New England J. Med. **255**: 164–169, 1956).

Summario in Interlingua

Esseva observate duo patientes in qui omne le criterios classic de sever anemia perniciose esseva presente sed in qui un normal capacitate de absorber vitamina B_{12} ab le vias gastrointestinal esseva demonstrate per medio de tests a vitamina B_{12} marcate per Co^{60}.

Ambe patientes monstrava le sequente symptomas e signos: Glossitis, diarrhea, vomito, disturbationes mental, generalisate debilitate progressive, sever anemia macrocytic, thrombocytopenia, grados moderate de leucopenia con hypersegmentate leucocytos polymorphonuclear, un megaloblastic medulla ossee, hyperbilirubinemia, e achlorhydria post histamina. Omne istos—excepte le achlorhydria—se resolveva completemente post administrationes parenteral de vitamina B_{12} e non ha recurrite intra un periodo de cinque menses.

Nos reporta iste casos proque illos es conforme a typic anemia perniciose in omne respectos excepte que le patientes esseva capace a absorber vitamina B_{12}.

Le presentia de thrombocytopenia e un tendentia hemorrhagic serviva a confunder le diagnose in iste patientes, ben que illo ha previemente essite describite como phenomeno in anemia perniciose per Nittis e alteros. Nos ha observate quatro patientes additional in qui le diagnose de anemia perniciose esseva initialmente obscurate per le presentia de thrombocytopenia.

Ambe nostre patientes, qui ambes habeva achlorhydria, haberea essite designate como casos de anemia perniciose mesmo ante le introduction del test del absorption de vitamina B_{12}. Le facto que ambes se monstrava capace a absorber vitamina B_{12} ab le vias gastrointestinal obliga nos a listar los como casos de "carentia probabile de vitamina B_{12}" resultante in manifestationes identic con anemia perniciose.

BIBLIOGRAPHY

1. Castle, W. B.: Observations on etiologic relationship of achylia gastrica to pernicious anemia. I. Effect of administration to patients with pernicious anemia of contents of normal human stomach recovered after ingestion of beef muscle, Am. J. M. Sc. **178**: 748, 1929.

2. Schilling, R. F.: Intrinsic factor studies. II. Effect of gastric juice on urinary excretion of radioactivity after oral administration of radioactive vitamin B_{12}, J. Lab. and Clin. Med. **42**: 860, 1953.
3. Schilling, R. F., Clatanoff, D. V., and Korst, D. R.: Intrinsic factor studies. III. Further observations utilizing the urinary radioactivity test in subjects with achlorhydria, pernicious anemia or a total gastrectomy, J. Lab. and Clin. Med. **45**: 926, 1955.
4. Davidson, C. S., Murphy, J. C., Watson, J. J., and Castle, W. B.: Comparison of the effects of massive blood transfusions and of liver extract in pernicious anemia, J. Clin. Investigation **25**: 858, 1946.
5. Nittis, S.: Blood platelets in pernicious anemia after liver therapy, Ann. Int. Med. **4**: 931, 1930–31.
6. Talbot, T. R.: Personal observations.
7. Mason, J. D., Jr., and Leavell, B. S.: The effect of transfusions of erythrocytes on untreated pernicious anemia, Blood **11**: 632, 1956.
8. Wintrobe, M. M., Cartwright, G. E., Palmer, J. G., Kuhns, W. J., and Samuels, L. T.: Effect of corticotrophin and cortisone on the blood in various disorders in man, Arch. Int. Med. **88**: 310, 1951.

CRYPTOCOCCUS MENINGITIS ARRESTED WITH AMPHOTERICIN B*

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The therapy of cryptococcosis remains a challenge, particularly when there is involvement of the central nervous system. A wide variety of drugs and agents has been used to combat this disease, presumably with successful results in rare instances, but usually without any effect upon the course of the infection. In recent years the antifungal antibiotics, Acti-dione and nystatin, have attracted particular attention. There have been several reports of recovery following the use of Acti-dione. However, after reviewing all the known cases treated with this drug, Carton [1] concludes that Acti-dione is not very effective against central nervous system cryptococcosis. As far as we can ascertain, no recoveries have been reported with nystatin. In an unpublished experience by one of us (E. A.) with the use of nystatin in two cases of cryptococcus meningitis, the drug was found to be ineffective.

More recently, two new antifungal antibiotics, amphotericins A and B, have been described.[2, 3, 4] They are derived from an unidentified Streptomyces species and are rather insoluble in water. Both amphotericins are active when administered parenterally or orally against a variety of fungi, but the B form is more active than the A against some of the yeasts and yeastlike fungi, including *Cryptococcus neoformans*. Acute toxicity from amphotericin B was shown to be of a

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From the Bureau of Laboratories, New York City Health Department, and from the Medical Service, Beth David Hospital.
Amphotericin B was supplied by E. R. Squibb & Sons, New Brunswick, New Jersey.
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very low order.[5] It seems worth while to report a case of cryptococcus meningitis in which clinical arrest appeared to follow the use of amphotericin B.

Case Report

History: A 46 year old white female laboratory technician was admitted to Beth David Hospital on May 22, 1956, with the complaints of headache, stiffness of neck, malaise, weakness and weight loss of approximately two months' duration. A month before admission the patient had become apathetic and somewhat incoherent, and subsequently quite disoriented. All of these symptoms became progressively worse. For about 20 years the patient had had diabetes, for which she had been treated with diet and insulin. There was no past history of rheumatic fever, syphilis or any other severe illness.

Physical Examination: On admission the patient was apathetic, incoherent and disoriented. The temperature was 100.4° F.; pulse rate, 92; respiratory rate, 18. The pupils were unequal; they reacted sluggishly to light and better in accommodation. Funduscopic examination showed tortuosity of the blood vessels, with some blurring of the discs and the presence of chorioretinitis on the right side. The lungs were clear. The heart did not appear to be enlarged. Auscultation revealed short systolic murmurs at the apex and base and a soft diastolic murmur along the left border of the sternum. The blood pressure was 180/80 mm. of Hg. The abdomen was soft; the liver and spleen were not felt. The pulse was Corrigan in type, and a positive Duroziez' sign was elicited. There was moderate nuchal rigidity, associated with positive Brudzinski's and Kernig's signs. An equivocal Babinski's sign was noted on the right side. The deep tendon reflexes were diminished and the superficial abdominal reflexes were absent.

Laboratory Examination: Urinalysis revealed a trace of sugar and a few red and white blood cells. The red blood cell count was 4,290,000, with 86% hemoglobin, and the white blood cell count was 8,000, with 68% polymorphonuclear leukocytes, 23% lymphocytes, 7% monocytes and 2% eosinophils. The blood chemistry showed a sugar of 177 mg.; urea, 10.3 mg.; creatinine, 1.05 mg.; uric acid, 2.65 mg.; calcium, 9 mg.; phosphorus, 3.3 mg.; cholesterol, 160 mg.; esters, 90 mg. per 100 c.c. The CO_2 combining power was 40 vol.%. The blood albumin was 4.8 and the globulin 1.45 gm. per 100 c.c. The sodium was 135 mEq./L., potassium, 4.3 mEq./L. Roentgenograms of the chest and skeletal system failed to reveal any abnormality. The electrocardiogram was essentially normal. The erythrocyte sedimentation rate was 51 mm. in one hour. The sputum was negative for acid-fast bacilli and for fungi. The blood culture was sterile. The Kolmer, Mazzini and the treponema immobilization tests were all negative. An intradermal toxoplasmin test was interpreted as positive. The spinal fluid was clear, with 120 cells, predominantly mononuclears, 74 mg. of protein, 76 mg. of sugar and 750 mg. of chlorides per 100 c.c., and was positive for *Cryptococcus neoformans* by culture (figure 1). The colloidal gold curve was 0112233221. Pathogenicity of the isolated organism was established by intraperitoneal mouse inoculation and recovery of the fungus from the blood and organs of the animals. The susceptibility of the fungus to antibiotics is shown in table 1. The pronounced sensitivity of the organism to amphotericin B is apparent.

Treatment and Course: Treatment with amphotericin B orally was instituted on June 8, 1956. The initial daily dose of the drug was 1.6 gm., given in divided amounts. The dosage of the drug was increased progressively until the patient was receiving 8 gm. daily. Despite the intensive treatment the patient's condition showed marked deterioration, with increased lethargy and disorientation and persistence of the cryptococci in the spinal fluid. The diabetic state, however, was kept under good control with diet alone.

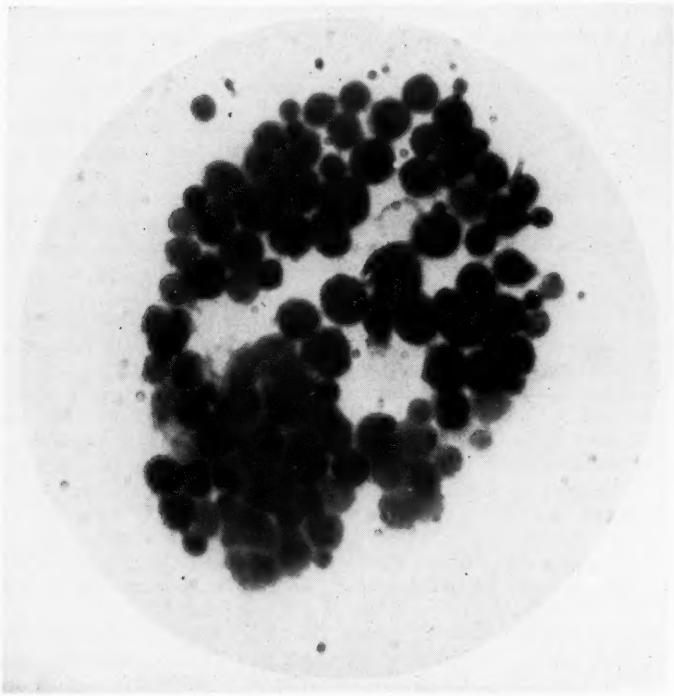

FIG. 1. *Cryptococcus neoformans* as seen stained, × 960. Note variability in size and budding forms.

Following five weeks of oral medication, with failure of response, it was decided to change to parenteral use of the drug. Accordingly, on July 12, 1956, the patient received intravenously 100 mg. of amphotericin suspended in 500 c.c. of 5% glucose in saline, administered slowly over a period of six hours. This form of treatment was

TABLE 1

Sensitivity of Isolated Cryptococcus to Antibiotics

Antibiotic	Concentration of Antibiotic in Micrograms per Milliliter Required to Cause	
	Inhibition of Growth	Sterilization of Culture
Penicillin	>500	>500
Streptomycin	>500	>500
Chlortetracycline	>500	>500
Oxytetracycline	>500	>500
Tetracycline	>500	>500
Chloramphenicol	>500	>500
Erythromycin	>500	>500
Carbomycin	>500	>500
Bacitracin	>500	>500
Neomycin	125	125
Polymyxin	0.45	0.45
Nystatin	0.9	1.9
Amphotericin B	0.01	0.02

given once daily for 12 days, and subsequently once every second day for about five weeks. The medication was discontinued on September 1, 1956.

Within two weeks following the institution of parenteral therapy there was evidence of clinical improvement, noted particularly in clearing of the sensorium. With continuation of this regimen there was progressive improvement, with defervescence and recession of the neurologic signs and symptoms. The diabetic state remained under control, although it occasionally required small doses of insulin. The endocardial murmurs and the peripheral signs of aortic regurgitation persisted. As will

TABLE 2

Cerebrospinal Fluid Observations

Date	No. of Cells	Predominating Type of Cell	Protein, mg./100 c.c.	*Sugar, mg./100 c.c.	Chlorides, mg./100 c.c.	Smear	Culture
5/28/56	120	Mononuclears	74	76	750	Negative	Positive cryptococci
6/4/56	71	Mononuclears	103	82	720	Negative	Positive cryptococci
6/19/56	110	Mononuclears	72	113	725	Positive cryptococci	Positive cryptococci
6/26/56	35	Mononuclears	88	89	738	Negative	Positive cryptococci
7/2/56	65	Mononuclears	56	85	750	Negative	Positive cryptococci
7/9/56	52	Mononuclears	82	76	725	Negative	Positive cryptococci
7/18/56	35	Mononuclears	58	150	750	Negative	Positive cryptococci
7/23/56	100	Mononuclears	64	131	750	Negative	Negative
7/31/56	30	Mononuclears	49	142	788	Negative	Negative
8/6/56	30	Mononuclears	58	129	750	Negative	Negative
8/13/56	20	Mononuclears	49	158	755	Negative	Negative
8/20/56	20	Mononuclears	63	99	775	Negative	Negative
8/27/56	30	Mononuclears	58	110	775	Negative	Negative
9/10/56	10	Mononuclears	58	75	775	Negative	Negative
9/24/56	30	Mononuclears	51	73	738	Negative	Negative

* The relatively high sugar determinations may be attributed to the patient's diabetic state.

be noted in table 2, the specimen of spinal fluid obtained on July 23, 1956, as well as all subsequent specimens, did not show the presence of cryptococci by smear or culture. Repeated blood cultures remained sterile.

At the time of her discharge from the hospital on September 26, 1956, the patient was in good physical and mental condition, and free of symptoms referable to the central nervous system. On follow-up seven months later she was found to be in the same satisfactory state.

It should be noted that during the administration of amphotericin B there was evidence of transitory impairment of renal function. This was shown by elevated

blood urea figures, ranging from 27 to 39 mg., elevated uric acid, ranging from 5.35 to 8.6 mg. and a rise in phosphorus to 7.4 mg. per 100 c.c. Following the termination of the antibiotic therapy these determinations reverted to normal. There were no other striking untoward effects, with the possible exception of one short episode of diarrhea.

Comment

In this case the diagnosis of cryptococcus meningitis was established by the spinal fluid studies. The results of the mouse inoculations furnished absolute proof that the organisms isolated from the spinal fluid were pathogenic. It is difficult to appraise the significance of the positive toxoplasmin test, unless one assumes that the patient had had toxoplasmosis at some time in the past. The association of chorioretinitis with that disease is well known. Since there was no history of rheumatic fever or evidence of a luetic infection, and since the blood cultures were consistently sterile, the nature and pathogenesis of the valvular heart lesions are matters of speculation. It is well to bear in mind that on rare occasions cryptococcosis may involve the heart, including the endocardium and valves.[6]

The tendency toward spontaneous remissions in cryptococcosis is well known and makes evaluation of drugs difficult. However, in the case reported here it would seem that arrest of the infection was related to the amphotericin. This is based largely on the marked sensitivity of the isolated organism to the drug and on the pronounced clinical and spinal fluid improvement observed shortly after the institution of the parenteral regimen. It must be admitted that the time that has elapsed since the termination of therapy is inadequate for a final appraisal of the drug.

It is of interest to note that the amphotericin was well tolerated by the patient in both the oral and the parenteral forms. The only untoward reactions noted were a short episode of diarrhea and evidence of transitory impairment of renal function, which was suggestive of nephrotoxicity.

Summary

In a case of cryptococcus meningitis, arrest of the infection apparently followed the parenteral use of amphotericin B. The drug was well tolerated, and there were no neurologic residua.

Summario in Interlingua

Le tractamento de cryptococcosis remane problematic, specialmente in casos in que le systema nervose central es afficite. Recentemente duo nove antibioticos antifungal ha essite describite sub le nomines de amphotericina A e amphotericina B. Ambes es active contra un varietate de fungos, sed le forma B es plus active que le forma B in destruer certe saccharomycetes e fungos saccharomycetoide, incluse *Cryptococcus neoformans.*

Es reportate un caso de meningitis a cryptococco tractate con amphotericina B. Le patiente esseva admittite al hospital con typic signos e symptomas de meningitis. In plus, il habeva signos de regurgitation aortic. Culturas de sanguine esseva sterile, sed le culturas de fluido spinal esseva positive pro *C. neoformans.* Omne reactiones pro syphilis esseva negative. Le patiente esseva primo tractate con amphotericina oral, sin ulle responsa. Tamen, le administration intravenose del droga esseva sequite

per un progressive melioration clinic, e le culturas de fluido spinal deveniva negative. A parte le persistente regurgitation aortic (de que le etiologia non esseva determinate), le patiente experientiava un apparentemente complete restablimento. Nulle evidentia de recidiva esseva notate durante plure menses sequente.

Il pare que le arresto del infection in le presente caso esseva conditionate per le administration parenteral de amphotericina. Iste assertion se basa principalmente super le marcate sensibilitate del isolate organismo al effectos del droga e super le pronunciate melioration del stato clinic e del fluido spinal que esseva observate brevemente post le institution del curso parenteral. Es a notar que le amphotericina esseva ben tolerate per le patiente.

BIBLIOGRAPHY

1. Carton, C. A.: Treatment of central nervous system cryptococcosis: a review and report of four cases treated with Acti-dione, Ann. Int. Med. **37**: 123, 1952.
2. Gold, W., Stout, H. A., Pagano, J. P., and Donovick, R.: Amphotericins A and B, antifungal antibiotics produced by a streptomycete. I. In vitro studies, *in* Antibiotics annual 1955–1956, 1956, Medical Encyclopedia, Inc., New York, p. 579.
3. Vandeputte, J., Wachtel, J. L., and Stiller, E. T.: Amphotericins A and B, antifungal antibiotics produced by a streptomycete. II. The isolation and properties of the crystalline amphotericins, *in* Antibiotics annual 1955–1956, 1956, Medical Encyclopedia, Inc., New York, p. 587.
4. Steinberg, B. A., Jambor, W. P., and Suydam, L. O.: Amphotericins A and B: two new antifungal antibiotics possessing high activity against deep-seated and superficial mycoses, *in* Antibiotics annual 1955–1956, 1956, Medical Encyclopedia, Inc., New York, p. 574.
5. Sternberg, T. H., Wright, E. T., and Cura, M.: A new antifungal antibiotic, amphotericin B, Antibiotics annual 1955–1956, 1956, Medical Encyclopedia, Inc., New York, p. 566.
6. Longmire, W. P., Jr., and Goodwin, T. C.: Generalized Torula infection: case report and review with observations on pathogenesis, Bull. Johns Hopkins Hosp. **64**: 22, 1939.

ACUTE PERICARDITIS AS THE FIRST MANIFESTATION OF INFECTIOUS MONONUCLEOSIS *

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Despite the publication in recent years of numerous case reports of acute nonspecific pericarditis, little progress has been made in defining its etiology. Clinical manifestations have been adequately reviewed.[1, 2, 3] The syndrome, sometimes following an upper respiratory infection, is characterized by anterior chest pain of pericardial origin, often with a pleuritic component which may be influenced by position. Moderate enlargement of the cardiac silhouette is common and is usually attributed to a small pericardial effusion. Pleural effusion may also occur. The electrocardiographic changes follow the typical evolutionary pattern of acute pericarditis.

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Infectious mononucleosis, on the other hand, is a disease of protean manifestations whose diagnosis may be established by a significant titer of the Paul-Bunnell heterophil test, following guinea pig kidney tissue absorption. Young adults are most frequently afflicted. Indications of myocardial involvement in infectious mononucleosis have been reported from time to time, chiefly in the form of electrocardiographic changes during the acute phase.[4, 5, 6] Nonspecific T-wave changes, for example, may occur. Sparse lymphocytic collections in the myocardium in the periphery of small blood vessels have been noted in those few cases which came to necropsy.[7] Leibowitz, in his recent monograph on infectious mononucleosis, has summarized the evidence of cardiac involvement.[8]

It is of interest that in the last nine years eight cases have been reported of acute pericarditis occurring in association with infectious mononucleosis. In 1946 Graybiel and Evans [6] reported four cases of infectious mononucleosis, with T-wave abnormalities in the electrocardiogram, during an epidemic at a Naval air station. One patient developed a pericardial friction rub on the fifth day of illness, with a low T-wave in Lead II and a partly inverted T-wave in Lead AVF. Another cadet developed precordial pain, fever, pericardial effusion and a friction rub in the presence of a positive heterophil test, with titer as high as 1:896 and marked lymphocytosis in the peripheral blood. This patient went into shock during the illness but recovered.

In 1951 De Fazio and Marsico [9] reported a case of infectious mononucleosis in a 42 year old man who developed left chest pain, cardiac enlargement and pericardial rub along with the serial electrocardiographic changes typical of acute pericarditis.

In 1953 Miller et al.[10] reported three cases of acute pericarditis in young people occurring in association with classic signs and symptoms of infectious mononucleosis. They reviewed the reported cases of this association. It is of interest that the signs of acute pericarditis preceded the manifestations of infectious mononucleosis by two weeks in two of their cases. All three patients had precordial pain, friction rub and electrocardiographic findings generally considered classic for acute pericarditis. The heterophil titers were diagnostically elevated in each case. The authors felt that the association of pericarditis and infectious mononucleosis was not merely coincidental, but postulated pericardial involvement by a viral agent either directly or by extension from the hilar nodes. The possibility of the pericardium's acting as a "shock organ" to an offending allergen was also mentioned.

Soloff and Zatuchni [11] in 1953 reported a case of acute benign pericarditis, manifested by the usual pain pattern and typical electrocardiographic features, but without a pericardial friction rub, in whom the finding of lymphadenopathy led to a detailed work-up. The typical blood changes of infectious mononucleosis were found, along with a highly significant rise in the heterophil titer. Transient atrioventricular nodal rhythm occurred in this patient. An electrocardiogram taken as long as four and a half months after the onset of illness still showed minor abnormalities, although clinical recovery was apparently complete at this time.

Kramer [12] observed a young man who developed acute pericarditis with effusion during the course of infectious mononucleosis. The electrocardiographic changes were classic for acute pericarditis. There was full recovery over the course of several months.

Our purpose is to present another instance of acute pericarditis, indistinguishable from the typical case of so-called acute nonspecific pericarditis, in whom the features of infectious mononucleosis later became evident.

Case Report

A 26 year old surgical intern was admitted to the New York Hospital on January 25, 1955, complaining of headache, generalized muscular aching and severe substernal pain. Headache and myalgia had been present for about three days. Severe crushing substernal chest pain, with radiation down the left arm, had awakened him from sleep on the morning of admission. There was a sense of bandlike constriction about the chest. Partial relief from pain was obtained by sitting in a bolt-upright position, or at the end of deep inspiration. There was no history of prior cardiovascular disease.

On physical examination the temperature was 38° C.; pulse, 90 and regular; blood pressure, 110/80 mm. of Hg; respirations, 18. The patient was normally developed, of stocky build, and in no immediate respiratory distress. There was no cyanosis. The pharynx was normal in appearance. A 1 cm., slightly tender left tonsillar node was the only significant lymphadenopathy detected. The heart was not enlarged to percussion. The tones were slightly distant but of good quality. The rhythm was regular. A faint systolic murmur was noted along the left lower sternal border. A pericardial friction rub was not heard. Lung fields were clear. Liver and spleen were not enlarged.

Examination of the blood disclosed a white blood cell count of 5,400 per cubic millimeter, with 34% lymphocytes. No atypical lymphoid forms were seen. There was no anemia. Urine was clear. Sedimentation rate was 13 mm. per hour (Wintrobe). A chest film revealed clear lung fields and unremarkable cardiac silhouette. A 12 lead electrocardiogram taken on the morning of admission revealed the typical changes of acute pericarditis, with elevated R-T segments in most leads (figure 1). A heterophil agglutination obtained on the second day of admission was borderline positive in a dilution of 1:128. One blood culture was sterile. Typhoid, paratyphoid and cold agglutinations were not elevated. An antistreptolysin titer was less than 25 units. The C-reactive protein was 2 plus, consistent with some degree of tissue inflammation.

The patient was considered to have acute nonspecific pericarditis and was kept on bed-rest without antibiotic therapy. He became afebrile and free of chest pain in five days. A friction rub never developed, and the cardiac silhouette remained within normal limits. The electrocardiogram evolved in a pattern typical of acute pericarditis, with return of the R-T segments to the iso-electric line and concurrent T-wave inversion in most leads (figure 1). On the fifth hospital day, however, differential white blood cell count showed 70% lymphocytes, of which 51% were atypical forms. On the seventh hospital day the patient developed tender, enlarged lymph nodes in the cervical, epitrochlear, axillary and inguinal regions. The pharynx became mildly injected, without exudate. Splenomegaly did not occur. At this time a heterophil agglutination of 1:3584 was obtained which was absorbed completely on beef red cells but not by guinea pig kidney tissue. The two abnormal findings from a series of liver function tests performed on February 1, 1955, were an alkaline phosphatase of 6.5 units (Bodansky), and bromsulphalein retention of 13.4% in 45 minutes. Treatment remained exclusively supportive, with analgesics as required and bed-rest. The clinical course was that of progressive improvement. By the time of discharge, on March 1, 1955, the generalized lymphadenopathy had subsided and liver function tests were within normal limits. However, the differential white blood cell count continued to show approximately 50% atypical lymphocytes, and the

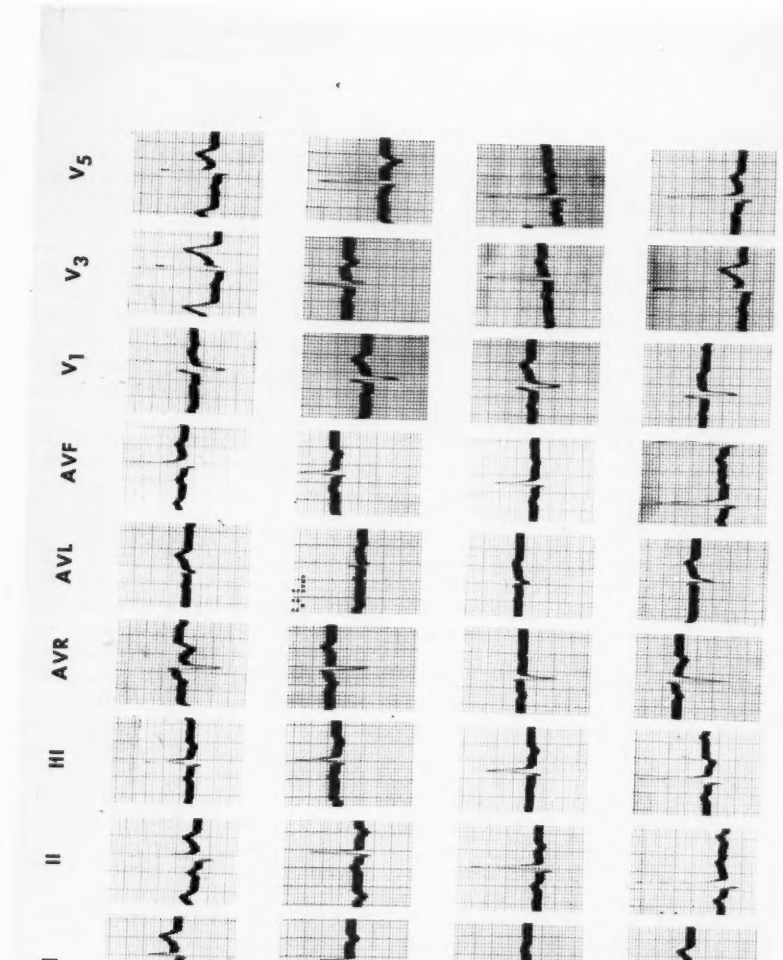

FIG. 1.

electrocardiogram remained slightly abnormal. After a two-week period of convalescence at home the patient was permitted to return to his hospital duties. On a further check, in April, 1955, the patient was found to be entirely asymptomatic and maintaining the full schedule of a surgical intern. The physical examination was negative. A chest x-ray was unremarkable. The heterophil test was 1:56, which was regarded as within normal limits. Slight elevation of the R-T segments in the electrocardiogram, however, persisted until May, 1955.

Comment

This is, we believe, the eighth reported case of acute pericarditis occurring in association with infectious mononucleosis. Anterior chest pain was characteristic of pericardial origin in its distribution and variation with respiration and body position. Electrocardiographic changes were confirmatory. It is noteworthy that the manifestations of pericarditis preceded signs of infectious mononucleosis by a full week, a sequence noted in some of the other reported cases. This fact, together with the mild nature of the infectious mononucleosis which ensued, could easily cause the latter diagnosis to be overlooked in other similar cases. In a syndrome so widespread as acute nonspecific pericarditis, and yet of such mysterious origin and pathogenesis, it is desirable that each newly discovered case be subjected to complete diagnostic study. For example, those tests should be employed that may help identify the more common viral agents, such as cold agglutinins and specific complement fixation tests. We would especially recommend serial heterophil agglutinations, as well as frequent perusal of the peripheral blood smear for atypical lymphocytes, to help detect underlying infectious mononucleosis.

Summary

1. Another case is reported of acute pericarditis occurring in association with infectious mononucleosis.

2. The signs of pericardial inflammation preceded the manifestations of infectious mononucleosis by one week.

3. The importance of a careful diagnostic survey is stressed in each instance of acute "nonspecific" pericarditis, including serial heterophil tests.

Summario in Interlingua

In le curso del passate nove annos, octo casos de pericarditis acute occurrente in association con mononucleosis infectiose ha essite reportate in le litteratura. Le presente articulo contribue un illustration additional de iste association.

Un interno de chirurgia de 26 annos de etate esseva admittite al Hospital New York con sever dolores thoracic substernal. Le examine physic esseva sin interesse. Nulle friction pericardial esseva notate. Tamen, le electrocardiogramma revelava le typic alterationes de acute pericarditis, e istos se disveloppava in le maniera usual. Le studios initial del sanguine esseva normal. Le quinte die del hospitalisation, lymphocytosis se disveloppava. Illo amontava a 70%, con 51% de formas atypic. Le septime die del hospitalisation, lymphadenopathia generalisate sin splenomegalia occurreva insimul con un leve pharyngitis. Esseva constatate un agglutination heterophilic de 1:3584 que se absorbeva completemente super erythrocytos bovin sed non super tessuto renal de porcos de India. Un phosphatase alcalin de 6,5 unitates (de Bodansky) esseva obtenite. Le retention de bromsulfaleina esseva 13,4% in 45 minutas. Le therapia esseva totalmente supportative. Le curso del morbo esseva

characterisate per restablimento rapide. Tamen, le electrocardiogramma remaneva levemente anormal durante un periodo de quatro menses.

Es signalate que in iste caso le manifestationes de pericarditis precedeva le signos de mononucleosis infectiose per non minus que un septimana. Il es possibile que iste facto ha causate le nonrecognition del diagnose de mononucleosis infectiose in altere casos del mesme genere. Es sublineate le importantia de un complete investigation diagnostic in omne caso de acute pericarditis "nonspecific." Le autores recommenda specialmente le obtention frequente de frottis de sanguine peripheric pro le detection de lymphocytos atypic e le effectuation serial de agglutinationes heterophilic como adjuta in le identification de subjacente mononucleoses infectiose.

BIBLIOGRAPHY

1. Carmichael, D. B., Sprague, H. B., Wyman, S. M., and Bland, E. F.: Acute nonspecific pericarditis: clinical, laboratory and followup considerations, Circulation **3**: 321–331, 1951.
2. Goyette, E. M.: Acute idiopathic pericarditis, Ann. Int. Med. **39**: 1032–1044, 1953.
3. Krook, H.: Acute non-specific pericarditis, Acta med. Scandinav. **148**: 201–218, 1954.
4. Wechsler, H. F., Rosenblum, A. H., and Sills, C. T.: Infectious mononucleosis: report of an epidemic in an Army post, Ann. Int. Med. **25**: 236–265, 1946.
5. Jaffe, H. L., Field, L. E., and Master, A. M.: Electrocardiogram in infectious mononucleosis, New York State J. Med. **48**: 1382–1385, 1948.
6. Evans, W. F., and Graybiel, A.: Electrocardiographic evidence of cardiac complications in infectious mononucleosis, Am. J. M. Sc. **211**: 220–226, 1946.
7. Custer, R. P., and Smith, E. B.: The pathology of infectious mononucleosis, Blood **3**: 830–857, 1948.
8. Leibowitz, S.: Infectious mononucleosis, Modern Medical Monographs, 1953, Grune and Stratton, New York, pp. 46–54.
9. De Fazio, V., and Marsico, F.: Complicanze cardiache nel corso della mononucleosi infettiva; un caso di pericardite, Progr. med., Napoli **7**: 545–550, 1951.
10. Miller, H., Uricchio, J. F., and Phillips, R. W.: Acute pericarditis associated with infectious mononucleosis, New England J. Med. **249**: 136–140, 1953.
11. Soloff, L. A., and Zatuchni, J.: Infectious mononucleosis associated with symptoms of acute pericarditis, J. A. M. A. **152**: 1530–1531, 1953.
12. Kramer, M. L., cited by Leibowitz, S.: Infectious mononucleosis, Modern Medical Monographs, 1953, Grune and Stratton, New York, p. 50.

PSEUDOHYPOPARATHYROIDISM: REPORT OF CASE*

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The interesting group of defects known as pseudohypoparathyroidism was first described by Fuller Albright [1] in 1942. His original report concerned three cases, and since that time an additional 14 cases have appeared in the world literature.[2-7] We wish to record one further case with observations relative to this disorder.

* Received for publication March 19, 1956.
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True parathyroid deficiency is characterized by chronic or recurrent tetany, low serum calcium, elevated serum phosphorus, lenticular opacities and calcifications in the basal ganglia. Pseudohypoparathyroidism possesses all of these same features but, in addition, is characterized by abnormalities of body build, facies and skeletal system, and by a strong tendency for ectopic calcification in the soft tissues. The diagnostic feature of pseudohypoparathyroidism is the failure to respond to the intravenous administration of parathyroid extract. In true hypoparathyroidism and, to a lesser extent, in normals, there is a prompt increase in the excretion of urinary phosphorus following parathormone injection. This procedure was first described by Ellsworth and Howard [8] in 1935, and is commonly referred to as the Ellsworth-Howard test. It is felt that the increase in tubular excretion of phosphorus which is stimulated by parathyroid hormone probably represents the basic function of the hormone in regulating the normal balance of serum calcium and phosphorus.

Individuals with pseudohypoparathyroidism show little if any increase in urinary phosphate following the administration of parathyroid extract. This finding has led to the present assumption that the defect responsible for the disorder is an inherent inability of the end organs to respond to endogenous secretion of parathormone. Whether the end organ is the renal tubule or bone matrix itself is not known, but it seems quite clear that the organism is incapable of responding to its own hormone. Exploration and biopsy of the parathyroid glands in this disorder have shown that they are neither hyperplastic nor atrophic, but rather normal in all respects.[1] Albright has suggested the analogy of pseudohypoparathyroidism to the Seabright-Bantam syndrome, in which the male rooster has female feathering in abnormal response to male hormone. He has further suggested the similarity of this disorder to those instances of low basal metabolic rates which do not respond to thyroid extract, and to the American Indian, with his notorious lack of beard despite normal androgen production.

The peculiar habitus, skeletal deformities and metastatic calcification of this disease, in addition to the predictable results of parathyroid insufficiency, led Albright [6] to speculate that there are at least three separate genetic defects, any one of which might be seen in the absence of the others. This now seems confirmed by the reports in the literature of those individuals with dyschondroplasia and metastatic calcifications in the presence of a normal serum calcium and phosphorus. This complicated syndrome has been rewarded with the intriguing title of pseudo-pseudohypoparathyroidism.[9, 10, 11]

Even though the pseudohypoparathyroid individual is incapable of responding to parathyroid extract, he is responsive in greater or less degree to such synthetic steroids as dihydrotachysterol (AT-10), calciferol or vitamin D. This responsiveness forms the basis for treatment of the disease. The oral administration of one of the above agents, plus added calcium salts and an agent to decrease phosphorus absorption from the gut, is used with success in relieving the hypocalcemic symptoms and restoring the individual to a semblance of normal existence.

Case Report

A 16 year old white female was admitted to St. Joseph's Hospital, Phoenix, Arizona, on August 22, 1955, with a one week history of abdominal pains, muscular aching, paresthesias, nausea and vomiting, and fever for 36 hours before admission.

It may be significant that her mother has retinitis pigmentosa, although her health otherwise and the father's health have been excellent. She has one brother, now age 12, in normal health. The mother states that the birth was normal and pregnancy uneventful save for moderate polyhydramnios. Immediately after birth the patient was recognized to have multiple congenital deformities, including kyphoscoliosis, cleft palate and bilateral club foot. Since the age of eight the child had been subject to "seizures," characterized by tonic contractions of the muscles and momentary lapses of consciousness. In the two years prior to her admission the seizures had become

FIG. 1.

so frequent as to be disabling, and she had almost constant trouble which the child described as "lazy muscles." There had been five previous hospital admissions since 1950 for cerebral concussion due to a fall, indeterminate abdominal pains, gastroenteritis and "epilepsy."

The most recent previous hospital admission was on August 3, 1955, for evaluation of her tonic, convulsive seizures. The spinal puncture at this time revealed a normal pressure with normal mechanics. The fluid was clear; protein, 46 mg.%; Pandy, negative; no cells; gold curve, 1233311000. An electroencephalogram was

reported as mildly abnormal with bouts of dysrhythmia. X-ray examination of the skull was reported as showing a "diffuse, calcified lesion in the anterior portion of the brain," with the possibility of calcified hemangioma to be considered. Films of the spine revealed multiple congenital anomalies, especially in the cervical area, with extensive kyphoscoliosis. The routine blood, urine and serologic test for syphilis were normal. The patient was dismissed from the hospital on August 8, 1955, diagnosis indeterminate, to continue anticonvulsant therapy.

She was re-admitted to the hospital on August 22 for the reasons noted at the start of the protocol. At this time it was our good fortune to observe the child with a typical tetanic seizure coincident with a crisis of abdominal pain and vomiting. Chvostek's sign was dramatically positive. There were pronounced mooning of the face, short flaring neck and short stature even more than could be attributed to the skeletal defects (figure 1). The hands were chubby to a mild degree.

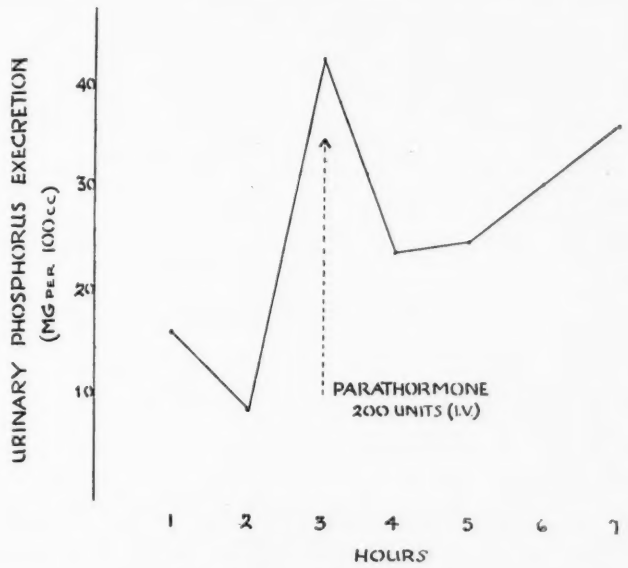

FIG. 2. Ellsworth-Howard test.

The serum calcium on August 23, 1955, was 5.9 mg.%; phosphorus, 8.0 mg.; carbon dioxide, 25.3 mEq./L. The hemoglobin measured 14.8 gm.; erythrocytes, 5.42 million; leukocytes, 14,850, with 74 neutrophils, 21 lymphocytes and 4 monocytes. The admitting urine showed 3 plus albumin, positive acetone, negative sugar, and 10 to 12 pus cells per high power field. After adequate hydration a repeat urine was normal, with no albumin or microscopic abnormalities. The nonprotein nitrogen measured 40 mg.%; creatinine, 0.55 mg.%. The serum albumin was 3.68 gm.%; globulin, 3.32 gm.%. X-ray examination of the skull showed diffuse calcification in the region of the basal ganglia. Films of the hands were normal save for some shortening of the fourth and fifth metacarpal bones of both hands. The electrocardiogram showed prolongation of the Q-T interval characteristic of hypocalcemia, but was otherwise normal.

An Ellsworth-Howard procedure was performed on August 30, 1955. Hourly

urine specimens were collected for three hours prior to the intravenous administration of 200 units of Parathyroid extract (Lilly). Following this, urine was collected in hourly specimens for four hours. Determination of the phosphorus content was carried out in the hospital laboratory. The results of this study are shown in figure 2. Oddly enough, the last hour's specimen of urine before the test dose of hormone contained the highest amount of phosphate of all the samples. The average phosphorus content in milligrams per 100 c.c. of urine was 22.6 prior to the injection, and 29.0 for the period after the injection.

Therapy was started on September 1, 1955, and consisted of 2.5 mg. dihydrotachysterol (Hytakerol—Winthrop) daily in liquid form, 20 gm. of calcium lactate daily in water solution, and a multiple vitamin supplement. There was immediate disappearance of the hypocalcemic symptoms. On September 12 the serum calcium had risen to 11.4 mg.; phosphorus, 7.7 mg. per 100 c.c. At this time the dose of Hytakerol was reduced to 5.0 mg. per week, and the use of Basaljel (Wyeth) to

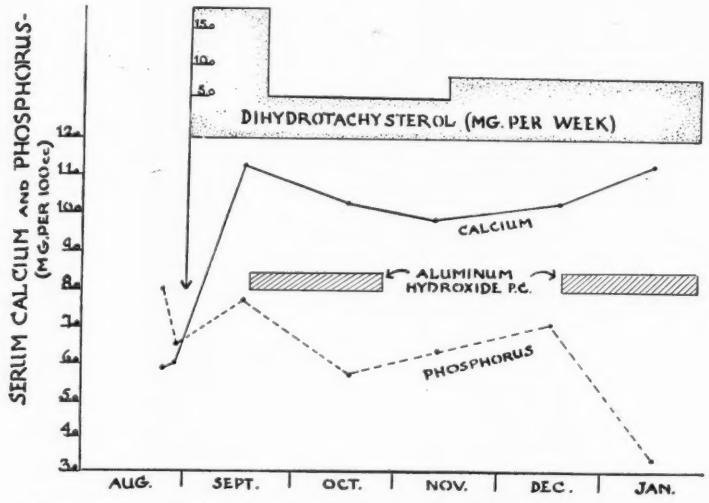

FIG. 3. Serum calcium and phosphorus values before and during therapy.

decrease phosphate absorption from the intestine was begun. Basaljel was discontinued after three weeks because of an individual intolerance and was replaced with Amphojel (Wyeth) for another week. On October 14 the serum calcium was 10.4 mg.%, phosphorus, 5.9 mg.%. Subsequent values can be seen from figure 3. Since November 20, the dose of Hytakerol has been maintained at 7.5 mg. per week in three divided doses. Amphojel was reinstituted on December 20 because of the high serum phosphorus values, and maintained since then in a dose of 10 c.c. with each meal. Either as a result of this or coincidentally, the serum phosphorus on January 10, 1956, had dropped to 3.4 mg., while the calcium measured 11.2 mg.

The patient has continued to be entirely free of all neuromuscular symptoms since the start of therapy. Most surprisingly, she has gained one and one quarter inches in height and five and one quarter pounds of weight in the six months since start of treatment. She has been mentally more alert and responsive, and is making good progress in remedial school work to catch up with her age group.

Summary

Pseudohypoparathyroidism is an unusual metabolic defect due, apparently, to end-organ failure to respond to endogenous parathyroid hormone. It is characterized not only by the predictable symptoms of hypocalcemia and hyperphosphatemia but also by curious anomalies of body structure and soft tissue calcification. A further case (the eighteenth in the literature) is reported in a 16 year old girl with studies pertinent to the metabolic defect and the response to therapy over a six month period.

Summario in Interlingua

Pseudohypoparathyroidismo es un rar disordine congenite del metabolismo, causate apparentemente per le incapacitate del organos terminal de responder al normalmente producite hormon thyroide. Le condition esseva primo describite per Albright in 1942. Depost ille tempore, 18 casos ha essite reportate. Pseudohypoparathyroidismo es characterisate per omne le tractos de ver carentia parathyroide—hypocalcemia con tetania, hyperphosphatemia, e calcification del gangliones basal—e in plus per anormalitates del statura corporee e calcification ectopic in le tessutos molle. Le morbo se distingue ab ver hypoparathyroidismo per le absentia de responsas al administration intravenose de extracto parathyroide (test de Ellsworth-Howard). Le tractamento de pseudohypoparathyroidismo require le uso de synthetic dihydrotachysterol o vitamina D, supplementos de calcium in forma solubile oral, e un agente appropriate que reduce le absorption de phosphoro ab le vias intestinal. Es reportate un caso de iste morbo, occurrente in un puera de 16 annos de etate, insimul con studios clinic e laboratorial pertinente al defecto metabolic in question.

BIBLIOGRAPHY

1. Albright, F., Burnett, C. H., Smith, P. H., and Parson, W.: Pseudohypoparathyroidism; an example of "Seabright bantam syndrome," Endocrinology **30**: 922–932, 1942.
2. Peterman, M. G., and Garvey, J. L.: Pseudohypoparathyroidism, Pediatrics **4**: 790–797, 1944.
3. Sprague, R. G., Haines, S. F., and Power, M. H.: Metabolic effects of parathyroid hormone, dihydrotachysterol and calciferol in a case of pseudohypoparathyroidism, J. Lab. and Clin. Med. **30**: 363, 1945.
4. Alexander, S. B., and Tucker, H. St. G.: Pseudohypoparathyroidism; report of case with late manifestations, J. Clin. Endocrinol. **9**: 862–873, 1949.
5. Bakwin, H., Gorman, W. F., and Ziegra, S. R.: Pseudohypoparathyroid tetany, J. Pediat. **36**: 567–576, 1950.
6. Elrick, H., Albright, F., Bartter, F. C., Forbes, A. P., and Reeves, J. D.: Further studies on pseudohypoparathyroidism: report of 4 new cases, Acta endocrinol. **5**: 199, 1950.
7. Oberst, B. B., and Tompkins, C. A.: Pseudohypoparathyroidism, Am. J. Dis. Child. **90**: 205–210, 1955.
8. Ellsworth, R., and Howard, J. E.: Studies on physiology of parathyroid glands. VII. Some responses of normal human kidneys and blood to intravenous parathyroid extract, Bull. Johns Hopkins Hosp. **57**: 91–98, 1935.
9. Albright, F., Forbes, A. P., and Henneman, P. H.: Pseudo-pseudohypoparathyroidism, Tr. A. Am. Physicians **65**: 337–350, 1952.
10. Miles, J., and Elrick, H.: Pseudo-pseudohypoparathyroidism, J. Clin. Endocrinol. and Metabolism **15**: 576–584, 1955.
11. Roche, M.: A case of pseudo-pseudohypoparathyroidism, J. Clin. Endocrinol. and Metabolism **15**: 964–969, 1955.

FATAL BROMSULPHALEIN REACTION *

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Since the introduction of bromsulphalein as a test for liver function by Rosenthal and White [1, 2] approximately 30 years ago, it has come to be considered a safe, innocuous and invaluable diagnostic clinical procedure.[3-7] Only rare toxic reactions without serious consequences have occurred.[8-13] The purpose of this paper is to report a fatal reaction to bromsulphalein (sulfobromophthalein, U.S.P.; phenoltetrabromphthalein-disodium sulfonate). To our knowledge, this is the first such case to be documented.

Case Report

A 58 year old married Indian laborer was first hospitalized from April 19, 1955, to May 16, 1955. His complaint at that time was intermittent acute abdominal pain, which he had had for several years. Clinical diagnoses were: (1) ureterocele, right, which we felt was causing intermittent obstruction of the ureter and a mild pyelonephritis; (2) marked obesity; (3) chronic alcoholism, and (4) fatty or portal cirrhosis of the liver. Bromsulphalein retention was 20% in one hour. He left against medical advice before the ureterocele could be treated.

The patient was re-admitted on August 23, 1955, with the chief complaint of "cough and hoarseness" of two weeks' duration. He had also had one recurrent episode of abdominal pain two weeks before, which had subsided spontaneously with symptomatic therapy by his local physician. Physical examination revealed a well developed, obese male with a normal temperature, a pulse rate of 90 per minute, and blood pressure of 154/104 mm. of Hg. There were a few inspiratory fine moist atelectatic râles at the base of both lungs, and distant generalized expiratory sonorous râles with a normal percussion note throughout. The remainder of the physical examination was essentially normal. A complete blood count and the chest x-ray were normal. Urinalysis was normal except for a trace of albumin. Sputum culture revealed gamma streptococcus, a nonhemolytic staphylococcus and *Neisseria flava.* The patient was diagnosed as having acute bronchitis and laryngitis. He responded to treatment with S-R penicillin (Parke, Davis Co.), 400,000 units daily. He was otherwise asymptomatic.

In order to reëvaluate his liver function, a bromsulphalein test was ordered. At 8:11 a.m. on August 31, 1955, 9.5 c.c. of a 5% solution of bromsulphalein were injected slowly intravenously. The exact length of time for the administration of the dye was not determined. Immediately after the injection the patient had no local or systemic symptoms. Several minutes later he moaned and complained of a frontal headache. He became cold and clammy, and his radial pulse became imperceptible. A sensitivity reaction was suspected immediately, but the patient died suddenly, before epinephrine and hydrocortisone hemisuccinate sodium could be administered intravenously. He had had no prior history of allergic diathesis.

Autopsy: Grossly † there was an abnormal amount of subcutaneous fat, which measured 7 cm. in thickness at the level of the umbilicus. The left lung weighed 480

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† Gross pathology reported by H. Charles Walker, Jr., M.D.

gm., the right lung, 420 gm. Dense adhesions obliterated the right pleural space. On inspection, palpation and cut sections of the lungs there were no apparent pulmonary, bronchial or intravascular pathologic lesions. The heart weighed 700 gm. It was surrounded by a massive amount of epicardial fat. The left ventricular wall measured 3 cm. in thickness, but the valves and coronary vessels were normal. The aorta contained atheromatous plaques. In the abdomen there was a large amount of perivisceral fat. The dome of the diaphragm was elevated to the level of the fifth anterior rib bilaterally. The liver weighed 1,900 gm. It was yellowish brown in color and had a smooth surface. On cut section it was greasy and firm in consistency. The spleen was very small; it measured 5 by 7 by 3 cm. and weighed only 50 gm. Its consistency was unusually soft. The cut surface scraped easily on cut section. The left kidney was small but weighed 160 gm. The lower pole of the kidney was irregular and scarred, but the capsule stripped easily. On cut section the cortex around the lower pole of the kidney was pale. The right kidney weighed 115 gm. It was scarred and covered with small retention cysts. There was a cystic dilatation at the right ureterovesical junction, with a small amount of purulent material above it. The brain was excessively wet and boggy. The cerebral vessels appeared congested.

Microscopic examination * of the liver revealed a marked degree of fatty metamorphosis, with large, empty vacuoles occupying a large proportion of the liver cells. The portal areas were slightly prominent. Multiple sections of the lungs revealed only slight congestion of the capillaries of the lung with blood. The right kidney showed areas with marked degree of tubular atrophy and mild chronic inflammatory infiltrate. A section of the urinary bladder taken to include the ureterocele revealed a normal bladder mucosa and a large cystic space in the muscular wall of the bladder which also had an epithelial lining. This was thought to represent a dilated ureter. Microscopic sections † of the brain revealed no abnormalities other than severe congestion of the cerebral vessels and some granular basophilic material in some of the vascular media consistent with the appearance of pseudocalcinosis. Routine sections of other organs were normal. Final pathologic diagnoses were: (1) obesity; (2) localized areas of pyelonephritis in the right kidney; (3) ureterocele of the urinary bladder, right; (4) very slight pulmonary congestion; (5) left ventricular hypertrophy; (6) essentially normal brain.

It is generally accepted that there are no recognizable pathologic tissue alterations that are, per se, invariably pathognomonic of allergy, either drug-induced or otherwise.[14] The clinical picture and necropsy findings indicate that bromsulphalein was an immediate constitutional sensitizing substance that brought on a fatal reaction, although absolute proof by demonstration of circulating antibodies is lacking.

Comment

Originally the bromsulphalein test employed the use of 2 mg. of the drug per kilogram of body weight.[1, 2] One of us (M. F. K.) has used the more reliable and sensitive 5 mg. per kilogram dosage [3] singly or serially for the past 10 years without encountering a single minor or major reaction. Except for transient reactions without unfavorable or prolonged after-effects, mentioned by Mateer et al.,[3] no serious reactions were recorded in the literature until 1948. Since then, six reports of such reactions with recovery have appeared in the literature.[8–13] Now for the first time, bromsulphalein must be added to the list of drugs [15, 16]

* Microscopic pathology reported by Donald F. Gleason, M.D., Veterans Administration Hospital, Minneapolis, Minnesota.

† Neuropathology reported by Maynard M. Cohen, M.D., Veterans Administration Hospital, Minneapolis, Minnesota.

known to have caused a fatal reaction. This incident bears out a statement of Barr's that not one of the occasionally indispensable diagnostic tests may be undertaken without a risk.[17] Even with the best intention and most correct practice, it must be realized that patients will occasionally be subjected to certain hazards, and physicians have to accept the risk if the invaluable benefits of modern diagnosis and therapy are to be appreciated.

It is not the intent of this report to discountenance or discredit a drug established as a diagnostic aid in clinical medicine. Evolutionary methods preventing the occurrence of another catastrophic reaction, no matter how remote, from the use of a well known drug demand consideration.

Cautions against repeating bromsulphalein tests without skin testing, desensitization or proper precautions for the management of a potentially dangerous allergic manifestation are a matter of record.[9, 13] However, it has been shown that skin testing is unreliable and desensitization impractical in protecting patients against possible penicillin anaphylactic reaction because of the lack of relationship between the intradermal reaction to various drugs and the patients' general reactions to them.[18, 19] Since bromsulphalein may be considered a hapten,[9, 15, 17] a similar conclusion may be deducted in regard to the handling of bromsulphalein. Some investigators, however, still urge the use of an intradermal test before repeating the bromsulphalein test, especially in patients with an allergic background.

It would appear that this reaction is an extremely rare example of the development of hypersensitivity occurring during a study in bromsulphalein tests performed at intervals. Personal communication with the manufacturers * revealed that the lots used had passed rigid tests for sterility, toxicity and pyrogen, and that no other complaints on 26,600 ampules included within the lots were received. Their brochure states "some physicians prefer the larger dosage schedule but reactions sometimes occur when the larger dose is used, particularly in heavy patients."

Several observers caution against rapid injection, and agree that the dye should be administered slowly over a five minute period.[8, 12, 13] Since the dye was injected slowly but without specific timing in this case, it is not known with certainty that slow intravenous administration of bromsulphalein will avoid the occurrence of other—occasional or rare—serious or fatal reactions, but it is a precaution worth heeding. It is suggested, therefore, that bromsulphalein be administered intravenously slowly by the clock over a period of five minutes. If an allergic diathesis is suspected, a skin test may be advisable before the bromsulphalein test is repeated. In addition, an epinephrine solution, 1 : 1000, should be available at the patient's bedside for immediate use if necessary.

Summary

A fatal allergic reaction to a bromsulphalein test is reported, with a discussion of precautionary measures.

Summario in Interlingua

Es reportate un reaction mortal a injection intravenose de bromsulfaleina (= sulfobromophthaleina, Pharmacopeia Statounitese, phenoltetrabromphthalein-disodium-

* Hynson, Westcott & Dunning, Inc., Baltimore, Maryland.

sulfonate), effectuate pro objectivos de testar le function hepatic in un masculo indian de 58 annos de etate. In tanto que constatabile, isto es le prime reporto de su genere documentate depost le introduction del colorante como adjuta diagnostic circa 30 annos retro. Durante iste periodo, solmente sporadic reactiones de toxicitate sin serie consequentias ha occurrite, de maniera que le uso de bromsulfaleina ha acquirite le reputation de un secur e innocue technica clinic del plus alte valor diagnostic.

Nove e medie centimetro cubic de un solution de 5% de bromsulfaleina (i.e. 5 mg per kg de peso corporee) esseva injicite. Le duration del administration del colorante non esseva mesurate, sed le processo esseva considerate como relativemente lente. Plure minutas plus tarde le patiente gemeva, se plangeva de mal de capite, e deveniva frigide, halituose, e apulsatile. Ante que mesuras de urgentia poteva esser applicate, ille moriva.

Le constatationes necroptic incriminava bromsulfaleina como substantia sensibilisante que evocava un immediate reaction constitutional que esseva mortal. Tamen, provas absolute in le forma de demonstration de anticorpore circulante non esseva obtenibile.

Le observation que acceptar le preciose beneficios del moderne methodos diagnostic e therapeutic non es libere de riscos pro le patiente merita esser repetite.

Pro evitar le repetition de iste rar sed catastrophic reaction, il es proponite que bromsulfaleina es administrate intravenosemente in le curso de cinque minutas chronometrisate e que un solution de epinephrina insimul con un injicibile corticosteroide es tenite preste al lecto del patiente pro uso immediate in caso de necessitate.

BIBLIOGRAPHY

1. Rosenthal, S. M., and White, E. C.: Hepatic function. A. The pharmacologic behavior of certain phthalein dyes. B. The value of selected phthalein compounds in the estimation of hepatic function, J. Pharmacol. and Exper. Therap. **24**: 265 (Nov.) 1924.
2. Rosenthal, S. M., and White, E. C.: Clinical application of the bromsulphalein test for hepatic function, J. A. M. A. **84**: 1112 (Apr. 11) 1925.
3. Mateer, J. G., Baltz, J. E., Marion, D. F., and MacMillan, J. M.: Liver function tests: general evaluation of liver function tests and appraisal of comparative sensitivity and reliability of newer tests, with particular emphasis on cephalin-cholesterol flocculation test, intravenous hippuric acid test and improved bromsulphthalein test with new normal standard, J. A. M. A. **121**: 723 (Mar. 6) 1943.
4. Barker, M. H., Capps, R. B., and Allen, F. W.: Chronic hepatitis in the Mediterranean Theater: new clinical symptoms, J. A. M. A. **129**: 653 (Nov. 3) 1945.
5. Popper, H., Steigmann, F., Meyer, K. A., Kozoll, D. D., and Franklin, M.: Correlation of liver function and liver structure, Am. J. Med. **6**: 278 (Mar.) 1949.
6. Greene, C. H.: Liver and biliary tract: survey of tests for hepatic function, use of hepatic star in differential diagnosis of jaundice, Arch. Int. Med. **86**: 743 (Nov.) 1950.
7. Suje, M., Kessler, B. J., and Lisa, J. R.: Clinical, functional and needle biopsy study of the liver in alcoholism, Arch. Int. Med. **86**: 658 (Nov.) 1950.
8. Chambers, W. N., and Moister, F. C.: Bromsulfalein reaction, Am. J. Med. **5**: 308 (Aug.) 1948.
9. Morey, G., Gabuzda, G. J., and Scudamore, H. H.: Sensitization to bromsulphalein (phenoltetra-bromphthalein-disodium sulfonate), Gastroenterology **13**: 246 (Sept.) 1949.
10. Sievers, J. J., Morey, G. E., and Samter, M.: Fixed anaphylactic sensitization, J. Allergy **20**: 76 (Jan.) 1949.
11. Roth, J. L. A.: Anaphylactoid reaction to sulfobromophthalein sodium, J. A. M. A. **143**: 802 (July 1) 1950.
12. de Andino, A. M., Jr., and McKeown, J. J., Jr.: Unusual toxic reaction to bromsulphalein, Ann. Int. Med. **34**: 1265 (May) 1951.

13. McVay, L. V., Jr.: Near fatal reaction to sulfo-bromophthalein (bromsulphalein) liver test, J. A. M. A. **152**: 1622 (Aug. 22) 1953.
14. Brown, E. A.: Problems of drug allergy, J. A. M. A. **159**: 814 (Mar. 5) 1955.
15. Flaxman, N.: Drug fatalities, J. A. M. A. **147**: 377 (Sept. 29) 1951.
16. Meyler, L.: Side effects of drugs, 1952, Elsevier Publishing Company, New York.
17. Barr, D. P.: Hazards of modern diagnosis and therapy—the price we pay, J. A. M. A. **159**: 1452 (Dec. 10) 1955.
18. Ryan, E. A., and Shouldice, E. E.: Allergy and procaine hydrochloride, J. A. M. A. **152**: 1554 (Aug. 15) 1953.
19. Berger, A. J., and Eisen, B.: Feasibility of skin testing for penicillin sensitivity, J. A. M. A. **159**: 191 (Sept. 17) 1955.

EDITORIAL

STANDARDS OF PRACTICE OF INTERNAL MEDICINE AND METHODS OF ASSESSING THE QUALITY OF PRACTICE IN HOSPITALS

A STUDY of this problem was initiated by the Regents of the American College of Physicians through a committee on Accreditation of Hospitals in Medicine,[1] not the Joint Commission on Accreditation. The committee elected to study the problem by surveying hospitals as a pilot study of present criteria and standards. The committee procured a Director who was to serve for one year,[2] but the committee functioned throughout in an advisory capacity. It was the purpose of the committee to "develop ways and means to define an acceptable standard for use by the Joint Commission on Accreditation, and secondly to judge the quality of internal medicine in American hospitals as practiced by physicians of all types." The Committee which planned and programed the survey decided that it should not be made by the Director or by any single individual. About 20 mature and experienced internists, all members of the American College of Physicians, were to survey 100 or more hospitals during the year. The surveyors were chosen largely from the personal friends and acquaintances of the committee and the Director.[3] They were selected to meet the geographic needs of the survey so that the entire United States could be covered without undue travel. No surveyor was to work in a hospital of his own neighborhood or where his influence might be felt. It was the considered plan of the committee that no surveyor should be briefed or instructed specifically in the technic of the survey. It was the hope of the committee that, by employing 21 different individuals, hitherto untried technics might be tested, and that individual initiative might develop the best form of hospital study. A member of the Advisory Committee described the instruction to each surveyor thus—that he should go to the hospital with this purpose and "play by ear" rather than by score. He was to report his observations in detail by letter. The Director of the survey, dismayed at the prospect of summarizing 20 such improvisings, did require each surveyor to record, on a form devised for key-sorting and hereafter referred to as a punch card, the results of his clinical record search, which was the only required part of his schedule. In the punch card method, observations could be recorded uniformly in a way that

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[2] Marion A. Blankenhorn, M.D., Cincinnati.

[3] Thomas Almy, M.D., William Bunn, M.D., Alex Burgess, M.D., Max Garon, M.D., Julian Kaufman, M.D., John C. Leonard, M.D., Joseph McCarthy, M.D., Frank McGlone, M.D., Lawrence Minish, M.D., S. M. Poindexter, M.D., Jack O. W. Rash, M.D., Truman Schnabel, M.D., Maurice Schnitker, M.D., Charley Smyth, M.D., Franz Stewart, M.D., Maurice Strauss, M.D., Arthur Colwell, M.D., C. Wesley Eisele, M.D., Eugene Ferris, M.D., and Murray Kinsman, M.D.

could be tabulated by the surveyor. Only hospitals described as "general medical and surgical for short-term care" were thus surveyed. The surveyors were men from a variety of experience and background. Fourteen were university teachers, most of whom were not full-time teachers. Fifteen had a subspecialty, and seven had no teaching affiliation whatsoever.

The choice of hospitals was made as representative as the Director could plan, so that large and small hospitals, hospitals connected with medical schools, and hospitals of varying ownership and sponsorship were chosen. It could be learned from available statistics that the greatest number of beds for general medical and surgical short-term care in the United States are found in hospitals larger than 100 and smaller than 300 beds. Therefore, more hospitals of this size were chosen. Only a few hospitals of less than 100 beds were surveyed; 14 hospitals with 500 or more beds were surveyed. The largest group of hospitals surveyed fell into the "other non-profit" category, of which there were 49. Twenty-five church-related hospitals were surveyed; four were church operated, 11 were city or municipality owned, two were state hospitals and three were owned by corporations.

Surveyors who volunteered for this chore were expected to apply one to two days to each hospital, and each was asked to inspect and record the results of a record search of 20 medical patients. Although no uniform method of procedure was furnished to the surveyors, it very soon developed that each man followed a somewhat similar pattern in his search. He would talk to the administrators of the hospitals and to the individuals responsible for ordering the affairs of internal medicine. This might be spoken of as "inspecting the workshop." He would then look at the laboratories, including x-ray, and look also to the special equipment which internal medicine requires, such as aspirators, respirators, spirometers, transfusion equipment, and various other devices. This might be called "inspecting the tools of the trade." His final chore was to look at the finished product of the shop, namely, the written record of patient care. To accomplish this, considerable help was required of the record librarian. The individual surveyor working with the record librarian would choose at random 20 different hospital charts which represented a wide selection of medical diseases, but were suitable to the punch card. The punch card grouped the medical diseases into six main groups. These groups are stroke, heart disease, diabetes, pulmonary infections, diseases of the blood, and liver and/or gastrointestinal disease. The record selection was made to cover as nearly as possible the diseases most commonly seen in hospitals which are generally known as medical diseases.

The record librarian, who was instructed in advance and was familiar with the punch card, was charged with the responsibility of making out the card by copying off certain items of information from her case records. The surveyor then took the punch card, together with the hospital record, and by his own devices looked through the hospital record and made out the

substance of his report, recording certain observations which he himself had made of this particular patient's record, as well as his final judgment about the quality of the care which that individual patient may have received. This was expressed as approved, not approved or partly approved. The individual surveyor was then requested to send these records—approximately 100, 20 from each of five hospitals—to the Director for analysis. The surveyor was requested to complete his cards and make his decisions while on the job and with the record in his hand. The surveyor was also requested to record, by running notes and comments in any form that he liked, the results of his survey of the hospital other than his record search. Most of the surveyors did very definitely arrange each of their five hospitals in the order of excellence, usually one hospital at the top and then two or three in the middle and one at the bottom.

TABLE 1

Correlation of Surveyors' General Assessment with Punch Card Analysis

	Hospitals Assessed by Surveyors as					
	Good		Fair		Poor	
Number of Hospitals	49	48%	33	32%	20	20%
Total Cards	997		644		387	
Total "Yes" Cards*	708	71%	369	57%	169	43%
Total "No" Cards*	73	7%	103	16%	77	20%
Total "Partly" Cards*	216	22%	172	27%	141	36%

* "Yes" cards are approved records.
"No" cards are not approved records.
"Partly" cards are partly approved records.

The director of the survey, in summarizing all of these reports, was able then to group all of the 102 hospitals into three groups, roughly defined as Good, Fair and Poor. If a surveyor did not arrange his hospitals in relative rank, deliberately, he was asked by correspondence to take his notes and do so. Meanwhile the Director, by a method of key-sorting inherent in the punch card system, was able to correlate the surveyor's judgment of case records with his judgment of the hospital as a whole. Now with all of the 102 hospitals being arranged in three groups, it was possible for the surveyor to take all of the punch cards from each group of hospitals and analyze them for the number that were approved, not approved, or partly approved. The degree to which these two categories of information could be correlated is shown in the accompanying bar graph (figure 1) as well as in table 1. Considerable information about the habits of medical practitioners can be gleaned from this study of 2,010 cards. Table 2 summarizes what the Director found most pertinent, or of general interest, or because of possible signifi-

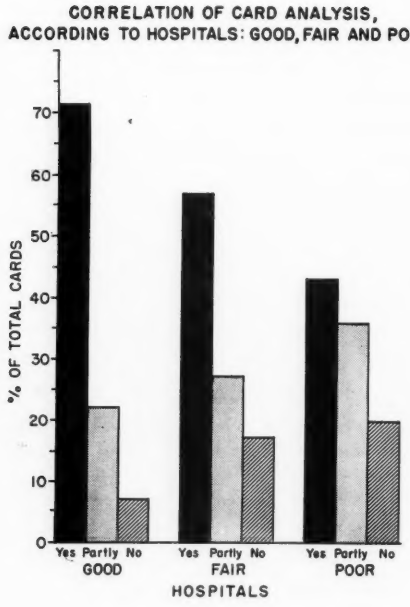

FIG. 1.

TABLE 2

Items of a General Nature from 2,010 Cards

Attending Physician			
Service	299	Number of Deaths	602
General Practitioner	807	Number of Autopsies	411
Internist	765		
Surgeon	130		
Other	48		
Blood Pressure Recorded	1851	Chest Film	1167
Weight	561	No. of Females	963
Urine Tested for Sugar	1858	Pelvic Examination	241
E.C.G.	935	Rectal Examination	562

Approved 1243 Not Approved 253 Partly 513

Specific Items Chosen at Random Because of Interest or Possible Significance

No. of Strokes	282	No. of Heart Diseases	488
With Retinoscopy	159	With E.C.G.	421
Under 50 Years	66	With Chest Film	311
With Lumbar Puncture	36	With Fluoroscopy	57
With Skull Film	20		
No. of Diabetics	301	No. of Diseases of the Blood	308
With Blood Sugar	286	With C.B.C.	292
With Retinoscopy	129	With Hematocrit	179
Urine Tested for Acetone	269	With Stool for Blood	79
		With Stool for Parasites	28

cance not necessarily signifying good or poor practice. Notable is the large proportion that had chest film, blood pressure, and urine tested for sugar. On the other side are the few females who had vaginal examinations recorded and the few with stroke examined with retinoscope or by lumbar puncture. What all this signifies in assessing the quality of medical care is not clear in this study. What it amounts to, in substance, is that hospitals classed as Good by the surveyor furnished the surveyor with charts which he generally could and did approve. At the same time, hospitals which have been classed as Poor furnished the surveyor with a goodly number of charts which were not approved. This correlation of the two methods, playing by ear or playing by score with the punch cards, is subject to statistical analysis. By the method of Chi Square a figure is developed which shows that the differences are highly significant, that is, that good hospitals have approved records and poor hospitals have a goodly number of not-approved records. It may seem futile to apply statistical methods to analyze data of this sort when we are well aware that there may be no difference between these two categories of judgment (i.e., by ear or by cards). It is true and quite possible that a surveyor working in a hospital which he classified as Good is prone to approve many of the hospital records, and the converse might be true. A conscientious surveyor—and most of them were extremely careful in their record search—can elaborate the reasons for not approving certain hospital charts. These reasons, as indicated on the punch card, are susceptible of review by the Director of the survey or by others. Whereas we might be guilty of making a statistical study of two methods of judgment, both made by the same person and possibly one being a repetition of the other, it is the belief of the Director of the Survey and the committee that analysis of the punch card does reveal clearly the reasons why medical practice in a given instance was not approved. There were 273 cards which recorded disapproval among 2,010 hospital records searched. Analysis of item 9 on the card, "Diagnosis Established," is not very revealing, and the same can be said for item 10, which has to do with medication. Item 11 shows that 41 autopsied cases were reviewed and 21 were disapproved because of wrong diagnosis. In item 12, "Hospital Stay," 98 out of 273 were disapproved as too short, only 18 as too long. Item 13 regards laboratory study, where 214 were disapproved as too little. The many specific reasons for disapproval, although well recorded, are too diverse to tabulate.

The results of punch card analysis can also be correlated with certain other factors which may modify hospital practice, which factors are easily assessed either by the surveyor or by direct inquiry by letter to the hospital itself. One of such factors is the presence or absence of a full-time pathologist, where it is clearly shown that the hospitals which have a full-time pathologist give a higher percentage of fully approved records. The same is true for the hospitals which have a full-time roentgenologist. The Director was unable to correlate the punch card analysis with such matters as the presence

or absence of a Director of Medical Service, or the presence or absence of a Chief of the Medical Service, or even a director of Medical Education. There is no clear definition of a Chief of Medical Service, Director of Medical Service, or Director of Mediçal Education, because any one of these three individuals may be giving only part-time duty in the hospital. The Director of the Survey could not correlate the quality of medical care with the presence or absence of any educational training program, such as an intern-resident training program. Fifty-eight of the hospitals which were surveyed did not have such training programs. Of the 58 hospitals, 20 were classed as good, 21 as fair and 17 as poor. The number of university hospitals that were surveyed was too few (six in fact) to have any statistical significance, and therefore no statement is made as to the classification of university hospitals, either by the method of generalities or by the method of card analysis. The same is true about any correlation between the ownership as to whether it is owned by state, county or city, or operated by the city, by the church, by an individual, and so forth. In correlating the size of hospitals by good, fair and poor, we find that most of the good hospitals lay in the 200 to 299 bed group. Most of the fair hospitals lay in the 300 to 499 bed group, and most of the poor hospitals lay in the 50 to 99 bed group. A study of the punch card reveals interesting information about the habits of practice in internal medicine in hospitals. A tabulated display with certain conspicuous features is shown in table 2.

Throughout this survey, individuals were advised to take no responsibility for any study of the educational program in the hospital. It was the feeling of the Advisory Committee that the surveyors would be fully occupied merely surveying the practice of internal medicine and not the teaching. Because each surveyor kept notes and reported the facts, it was gratifying to the Director to learn the cordial acceptance by the hospitals of just "another inspection." A few of the surveyors felt considerably baffled by undertaking such a nebulous quest, but when it had been done each seemed to feel he had learned much about his hospitals, and could and did make firm decisions.

It should be stated here that surveyors were paid a very moderate per diem and a limited amount to cover travel expenses. It was not a profitable job to any one when compared to the income received for the same time spent in practice. It also was comforting to the committee and to the Director to learn by letter the gracious manner in which the surveyors were treated in the individual hospitals. The original contact to come into the hospital and make the survey was made by letter from Dr. Babcock, of the Joint Commission on Accreditation, explaining the nature of the experiment and asking that the privilege be granted to the American College of Physicians. Both the letters of each surveyor and letters from hospital administrators show hearty and cordial coöperation in this study. A good many of the surveyors did write reports in the way of a feedback of suggestions to their particular hospitals.

The Director believes that the following opinions prevail in the minds of the 21 surveyors:

1. That the study of enough records by an expert will reveal good or bad medical care quantitatively in a given hospital.
2. That examination of the staff organization and its activities will reveal how a particular grade of practice is accomplished.
3. That to maintain good practice, practice of high standards, an inside audit is the most favored in particular reference to hospital deaths.

The Director of the survey observed that, although lengthy reports were made, no surveyor attempted to describe a standard whereby he was able to measure the quality of practice; although each surveyor was asked to invent, develop or discover some magic formula, no such formula has appeared. Nevertheless, each surveyor did give a firm opinion about each hospital he surveyed as to quality of medical care they were practicing. Furthermore, in individual instances, with hospital records before him, he did give a firm opinion as to whether management of this particular patient was approved, not approved, or partly approved, and hence could be classed as good, poor or fair. It now appears to the Director of this survey that each individual surveyor used his own methods of practice as a standard in making such judgments.

It is pertinent here to say that this survey is by no means the first attempt physicians or medical administrators have made to measure the quality and to devise standards of medical practice. A few such previous efforts may be cited here. Recently a Medical Audit has been devised and described in the ANNALS OF INTERNAL MEDICINE under the title, "Can the Quality of Medical Practice be Evaluated?" [4] Participating hospitals and their staffs could, by this audit, be arranged each in the order of excellence according to a formula in possession of the auditor. Another publication which could be cited is "Measuring the Quality of Medical Care Through Vital Statistics Based on Hospital Service Areas: 1. Comparative Study of Appendectomy Rates," by Paul A. Lembcke, M.D., who said: "It is usual to express the quality of medical care in terms of qualifications of personnel, adequacy of equipment, and the technical excellence of medical services performed. The best measure of quality is how closely the result approaches the fundamental objectives of prolonging life, relieving distress, restoring function, and preventing disability. Measurement of quality should be expressed in terms that are uniform and objective, and that permit meaningful comparisons between communities, institutions, groups and time periods, and with general standards." Most of these studies have been of surgical problems, or a very narrow zone of medical practice.

Certain organizations which have to do with the purchasing and the distribution of medical care, such as the Health Insurance Program, H.I.P.,

[4] Eisele, C. W., Slee, V. N., and Hoffmann, R. G.: Can the practice of internal medicine be evaluated? Ann. Int. Med. **44**: 144–161 (Jan.) 1956.

in New York City, have been concerned with quality. The Director of the H.I.P., Dr. George Baehr, has informed the Director, in personal communication and with reprints describing their activity, that medical practice is assessed by experts in internal medicine who go into the field and watch the practitioner at work, or judge the practioner by his hospital records. This same method is employed by another large "third party purchaser" of medical service, namely, the United Mine Workers Welfare Fund. Personal communication from Dr. John Morrison, their medical director, states that they have no way of assessing the quality of medical care except by inspecting the practitioner and his records, which inspection is done by experts in internal medicine.

If now a statement is to be made about standards in internal medicine, which the American College of Physicians suggests to the Joint Commission, the following may be offered: "Since we are unable to devise a measurement of quality expressed in terms that are uniform and objective, we propose the following in lieu of such measurement expressed in general terms. The American College of Physicians suggests that a minimal standard is such medical care as its mature and experienced members will approve in specific instances. The College approves a practice where patients with medical disorders which cannot be managed at home are sent to hospital, are examined, diagnosed and treated after the manner taught in medical colleges of the United States, and as described in textbooks of internal medicine. For approval, the College requires that sufficient record be kept by physicians to show proof of such care, a record that will be of value to the patient in subsequent disease and of value to the hospital administration in meeting the needs of the community. For the approval of the management of obscure and difficult conditions, the record must show that special medical care has been employed, that is, beyond the ordinary care, skill and diligence such as has been exercised by physicians and surgeons in that community, unless the circumstances were such that care was not available."

Marion A. Blankenhorn, M.D., Director,
Study of Hospital Standards of Practice in
Internal Medicine, American College of
Physicians, 1956–57.

REVIEWS

Functions of Autonomic Transmitters. By J. Harold Burn, M.D. 228 pages; 21 × 14 cm. The Williams & Wilkins Company, Baltimore. 1956. Price, $5.00.

This volume is the thirteenth in a series of the Abraham Flexner lectures given in the School of Medicine of Vanderbilt University. There were seven lectures, and in the first one Dr. Burn treated the subject of medical education and medical science, and brought out many differences in medical education in England and in America. The second lecture dealt with the historical observations of acetylcholine and the heart, and also some of the more recent work that Dr. Burn has engaged in concerning the effect of acetylcholine on cardiac muscle aside from its inhibitory effect through its cholinergic action. The third lecture dealt with ciliary movement with special reference to the neurohormones acetylcholine and norepinephrine. The fourth lecture concerns the action of norepinephrine with particular reference to its significance in the body. The fifth lecture is somewhat different, dealing with the common properties of different classes of drugs, for example, those drugs that elicit a quinidine-like action, those that produce hypothermia, and so forth. The sixth lecture dealt with the sensitivity of denervated structures, beginning with the early work of Budge, the work of Cannon, and some of the most recent contributions to the theory of denervated structural sensitivity. In the last of the seven lectures Dr. Burn dealt with the pharmacology of nicotine and alcohol, with special reference to their sociological implications.

On the whole the lectures were timely and well written, and embrace much of the interesting work of their author. In addition they show marked felicity of diction in expressing his thought.

John C. Krantz, Jr.

Practical Pediatric Dermatology. By Morris Leider, M.D., Associate Professor of Dermatology and Syphilology, New York University Post-Graduate Medical School. 433 pages; 25.5 × 17.5 cm. The C. V. Mosby Company, St. Louis, Mo. 1956. Price, $10.50.

This excellent text on *Practical Pediatric Dermatology* is a worthy addition to the existing literature on skin diseases. The importance of this work is amplified by a documented statement, in the preface, to the effect that every seventh case admitted to a large pediatric hospital was a cutaneous condition. The author has emphasized the practical aspects of diagnosis and treatment.

A helpful feature is the inclusion of a glossary of common words, terms, and phrases used in dermapathology. For practical purposes, the author has included a series of tables which are excellent diagnostic aids to general practitioners and pediatricians. The annotated formulary which occupies 20 pages should be of value to any practicing physician. The relationship of cutaneous lesions to systemic diseases is constantly stressed. Many of the photographs are lacking in detail, but this may be due to the fact that it is difficult to draw definitive focus on infant subjects. This text is to be generally recommended for use by general practitioners, pediatricians, and dermatologists.

H. M. R., Jr.

Paper Electrophoresis: Ciba Foundation Symposium. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and ELAINE C. P. MILLAR, A. H.-W.C., A.R.I.C. 224 pages; 21 × 14 cm. Little, Brown and Co., Boston. 1956. Price, $6.75.

Paper electrophoresis has become an important diagnostic tool. Since the results obtained by this technic vary with the type of apparatus used and with the methods of quantitation, it is frequently difficult to compare the results obtained from different laboratories.

At Dr. Durrum's suggestion, a meeting of a group of investigators in this field was arranged with the hope that some of the procedures might be standardized. This volume consists of the proceedings of this meeting. Twenty-two persons presented papers and participated in the discussions. They represented institutions in the United States, Britain, Germany, Norway, Sweden as well as other countries. The topics covered included general methods of paper electrophoresis and their application to biochemical and clinical problems; separation of human hemoglobins; evaluation of albumin-globulin ratio; effect of ACTH and cortisone on serum-bound polysaccharides; and the physicochemical aspects of apparatus design. The discussion following each paper is completely reported.

This volume should be useful as a reference to anyone working in this field.

M. A.

Clinical Unipolar Electrocardiography. 3rd Ed. By BERNARD S. LIPMAN, M.D., and EDWARD MASSIE, M.D. 397 pages; 22.5 × 14.5 cm. The Year Book Publishers, Inc., Chicago, Ill. 1956. Price, $7.50.

This is the third edition of this book on clinical electrocardiography. To the earlier editions, the authors have added information on congenital heart disease, ventricular gradient, vectorcardiography and vectorelectrocardiography. In addition illustrative electrocardiograms covering the various types of congenital and acquired cardiovascular lesions submitted to surgical correction have been included.

As in the earlier editions, the attempt has been made to present a simple and practical monograph intended primarily for those inexperienced in the field of electrocardiography. The figures are clear and the electrocardiograms well reproduced. Although one may differ in many details and in the interpretation of several of the electrocardiograms, the authors appear to have achieved their purpose in writing a practical monograph on electrocardiography for the inexperienced beginner.

L. S.

Proceedings of the Annual Meeting, Council for High Blood Pressure Research—1955. Volume 4. 186 pages; 23.5 × 15 cm. American Heart Association, New York. 1956. Price, $4.50.

This volume contains all eight papers presented at the 1955 meeting of the Council for High Blood Pressure Research of the American Heart Association. Hemodynamic studies of the splanchnic circulation are discussed by Dr. Stanley Bradley. Dr. W. J. Kolff integrates Dr. Arthur Grollman's renoprival hypertension with the observation "renin and angiotonin may have their effect not as direct pressor substances, but by impeding the blood pressure reducing or regulating function of the kidneys." The interplay of neurogenic and humoral factors in control of vascular tone and their relationship to autonomic blockade is discussed by Drs. A. A. Brust and E. B. Ferris. The rôle of trace metals in hypertension and atherosclerosis is

summarized by Drs. Perry and Schroeder. The remaining half of the report is devoted to a "neurovascular symposium" presenting studies demonstrating the interrelationship between the central nervous system and cardiovascular activity.

While some of the material is obsolete, this monograph will serve as an orienting point for contemporary concepts in the pathogenesis of hypertension. A bibliography and discussion accompany each paper.

The Proceedings deserve to be studied by those interested in hypertension and vascular disease.

F. B.

Clinical Urology (in two volumes). 3rd Ed. By OSWALD SWINNEY LOWSLEY, A.B., M.D., F.A.C.S., F.I.C.S., and THOMAS JOSEPH KIRWIN, M.A., M.S., M.D., F.A.C.S., F.I.C.S. 999 pages (both volumes); 29 × 22.5 cm. The Williams & Wilkins Co., Baltimore. 1956. Price, $32.50.

Clinical Urology by Lowsley and Kirwin is a two volume third edition. This very complete presentation on the subject of urology in general has been brought up to date and many changes are apparent. This has been a monumental task representing an enormous amount of "time, thought and energy." The new subject matter included has been made very attractive with many photographs and new illustrations by the great artist, Mr. William P. Didusch.

The structural form has been changed from the original editions to three columns to a page. This has enabled the authors to condense this vast amount of information into two volumes, but it has the drawback of being harder to read continuously than the bold type of the earlier editions where single columns were used.

There are 35 chapters in the two volumes. The striking things are the new methods of therapy including the use of antibiotics and, in fact, all of the other drugs useful in urinary tract infections. The latest developments in hormonal therapy are also available in this book. With the excellent illustrations, photographs, pen and ink sketches and beautiful drawings, operations on the urinary tract are made clear for both the urological surgeon and the general surgeon. Among these operations are the very latest operative procedures concerned with the diversion of the urinary stream necessitated by cancers of the urinary tract. The use of the artificial kidney is also explained in great detail.

It is difficult to see, with these two volumes on urology available, how any urologist or general surgeon can be without this edition. Also this edition will be in practically every library because for a long time it will have tremendous use as a reference. The index is complete and the bibliography is enormous. This bibliography is of particular value in pursuing research work in practically every phase of urology.

W. H. T.

Pediatrics. Edited by DONALD PATERSON, M.D., and JOHN FERGUSON MCCREARY, M.D., with 36 contributing authors. 654 pages; 26 × 18 cm. J. B. Lippincott Co., Philadelphia. 1956. Price, $14.00.

This is a very good book. In 654 pages, about half the length of the older standard textbooks, it presents nearly all that a textbook of pediatrics should include. Its shortness is confusing occasionally but usually improves the clearness of its presentations. This is especially true of the fine sections on fluid and drug therapy. The preface mentions a chapter on Tropical Pediatrics which I did not find in the table of contents. This subject should be discussed fully in later editions, since

physicians in the tropics must rely on textbooks from the temperate zones. The illustrations and printing are excellent.

Medical textbooks should be shorter. A medical curriculum may call for selecting out and learning the valuable information from more than 13,000 pages of textbooks. This new book may help to make the medical student's job more nearly possible.

G. S. C.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Alcoholism: A Treatment Guide for General Practitioners. By DONALD W. HEWITT, M.D. 112 pages; 20.5 × 14 cm. 1957. Lea & Febiger, Philadelphia. Price, $3.00.

Annual Review of Medicine. Vol. 8. DAVID A. RYTAND, Editor, Stanford University School of Medicine; and WILLIAM CREGER, Associate Editor, Stanford University School of Medicine. 530 pages; 23 × 16 cm. 1957. Annual Reviews, Inc., Palo Alto, California. Price, $7.00.

BCG Vaccination Against Tuberculosis. By SOL ROY ROSENTHAL, M.D., Ph.D., Director, Institution for Tuberculosis Research of the University of Illinois, etc.; with sections by DR. CAMILLE GUÉRIN, Honorary Chief of Service, Institut Pasteur, Paris; DR. BERNARD WEILL-HALLÉ, Honorary Director, School of Puericulture, etc.; and DR. ARVID WALLGREN, Professor of Pediatrics and Head of the Pediatric Clinic, Royal Caroline Institute of Medicine, Norrtull's Hospital, Stockholm. 389 pages; 24.5 × 16 cm. 1957. Little, Brown & Company, Boston. Price, $7.50.

Bioenergetics. By ALBERT SZENT-GYÖRGYI, The Institute for Muscle Research of the Marine Biological Laboratory, Woods Hole, Massachusetts. 143 pages; 22 × 14.5 cm. 1957. Academic Press, Inc., New York. Price, $4.50.

The Changing Patient-Doctor Relationship. By MARTIN G. VORHAUS, M.D., F.A.C.P.; drawings by A. BIRNBAUM. 310 pages; 22 × 14.5 cm. 1957. Horizon Press, New York. Price, $3.95.

Clinical Roentgenology of the Digestive Tract. 4th Ed. By MAURICE FELDMAN, M.D., Assistant Professor of Gastroenterology, University of Maryland, etc. 776 pages; 26 × 18 cm. 1957. The Williams & Wilkins Company, Baltimore. Price, $15.00.

Diagnosis and Treatment of Cardiovascular Disease. 5th Ed., in two volumes, boxed. Edited by WILLIAM D. STROUD, M.D., F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine; and MORRIS W. STROUD, III, M.D., Associate Professor of Medicine, Western Reserve University; with 30 contributors. 743 pages, Vol. I, 705 pages, Vol. II; 27 × 18.5 cm. (loose-leaf, leather-bound). 1957. F. A. Davis Company, Philadelphia. Price, $35.00.

Epilepsy: Grand Mal, Petit Mal, Convulsions. By LETITIA FAIRFIELD, C.B.E., M.D., D.P.H. 159 pages; 19 × 12.5 cm. 1957. Philosophical Library, Inc., New York. Price, $4.75.

Essays in Metabolism: The John Punnett Peters Number of The Yale Journal of Biology and Medicine. Edited by LOUIS G. WELT, M.D., Professor of Medicine, University of North Carolina School of Medicine, Chapel Hill. 382 pages; 26 × 17 cm. 1957. Little, Brown and Company, Boston. Price, $6.50.

La funzione corticosurrenale nella gravidanza normale. Società Italiana di Endocrinologia. VI Congresso Nazionale, Bari—10–11 Novembre 1956. By F. CASSANO and C. TARANTINO, with the collaboration of L. CIAMPALINI. 168 pages; 24.5 × 17.5 cm. (paper-bound). 1957. Società Italiana di Endocrinologia, Istituto di Patologia Medica dell'Università di Pisa. Price, 1200 Italian lire.

Gifford's Textbook of Ophthalmology. 6th Ed. By FRANCIS HEED ADLER, M.D., William F. Norris and George E. Deschweinitz Professor of Ophthalmology, University of Pennsylvania Medical School, etc. 499 pages; 24.5 × 16 cm. 1957. W. B. Saunders Company, Philadelphia. Price, $8.00.

Hemorrhagic Diseases. By ARMAND J. QUICK, Ph.D., Professor of Biochemistry, Marquette University School of Medicine. 451 pages; 24 × 16 cm. 1957. Lea & Febiger, Philadelphia. Price, $9.50.

Herz- und Gefässerkrankungen: Neue Wege Einer Funktionellen Differentialdiagnose (Kreislauf-Bücherei, Band 16). Von PROF. DR. R. VÖLKER; mit einem Geleitwort von PROF. DR. R. SCHOEN. 166 pages; 23 × 15.5 cm. 1957. Verlag von Dr. Dietrich Steinkopff, Darmstadt; available through Intercontinental Medical Book Corporation, New York. Price, brosch. DM 32.50; geb. DM 34.50.

Human Cancer: A Manual for Students and Physicians. By MAURICE M. BLACK, M.D., Associate Professor of Pathology and Clinical Pathology, New York Medical College, Flower and Fifth Avenue Hospitals; and FRANCIS D. SPEER, M.D., F.A.C.P., Professor and Director, Department of Pathology and Clinical Pathology, New York Medical College, Flower and Fifth Avenue Hospitals. 273 pages; 20 × 14 cm. 1957. The Year Book Publishers, Inc., Chicago. Price, $7.50.

Hutchison's Clinical Methods. 13th Ed. By DONALD HUNTER, M.D., F.R.C.P., Physician to the London Hospital; and R. R. BOMFORD, D.M., F.R.C.P., Physician to the London Hospital. 452 pages; 19 × 13 cm. 1957. J. B. Lippincott Company, Philadelphia. Price, $6.00.

International Congress of Gastroenterology: Fifth Meeting of L'Association des Sociétés Européennes et Méditerranéennes de Gastro-Entérologie, London, July 18–21, 1956. (Reprint from *Gastroenterologia,* Vol. 86, Nos. 3, 4 and 5, 1956.) 764 pages; 25 × 17.5 cm. 1957. S. Karger, Basel.

Lehrbuch der Inneren Medizin. Band I und II. 4., Vollig Neubearbeitete Auflage. Von M. BROGLIE, Neumünster; H. DENNIG, Stuttgart; K. HANSEN, Lübeck; W. GRONEMEYER, Bad Lippspringe; F. GROSSE-BROCKHOFF, Düsseldorf; N. HENNING, Erlangen; A. HEYMER, Essen; H. REINWEIN, Kiel; F. SCHELLONG; G. SCHALTEN-

BRAND, Würzburg; H. SCHULTEN, Köln; herausgegeben von HELMUT DENNIG, Stuttgart. Band I, 920 pages; Band II, 889 pages; 24.5 × 18 cm. 1957. Georg Thieme Verlag, Stuttgart; available in U.S.A. and Canada from Intercontinental Medical Book Corporation, New York. Price, Band I, Ganzleinen DM 52.–; Band II, Ganzleinen DM 52.–

The Leukemias: Etiology, Pathophysiology, and Treatment. Henry Ford Hospital International Symposium. Edited by JOHN W. REBUCK, Division of Hematology, Department of Laboratories, Henry Ford Hospital, Detroit; FRANK H. BETHELL, The Thomas Henry Simpson Memorial Institute for Medical Research, Ann Arbor; and RAYMOND W. MONTO, Division of Hematology, Department of Medicine, Henry Ford Hospital, Detroit. 711 pages; 24 × 15.5 cm. 1957. Academic Press, Inc., New York. Price, $13.00.

Lupus Nephritis. By ROBERT C. MUEHRCKE, M.S., M.D., Postdoctoral Public Health Fellow in Internal Medicine, Research and Educational Hospitals, University of Illinois College of Medicine, etc.; ROBERT M. KARK, F.R.C.P., F.A.C.P., Professor of Medicine, University of Illinois College of Medicine, etc.; CONRAD L. PIRANI, M.D., Professor of Pathology, University of Illinois College of Medicine, Chicago; and VICTOR E. POLLACK, M.B., M.R.C.P.E., Research Fellow in Medicine, Presbyterian Hospital, etc. 145 pages; 26 × 17.5 cm. 1957. The Williams & Wilkins Company, Baltimore. Price, $3.00.

Martius' Gynecological Operations, With Emphasis on Topographic Anatomy. Translated and Edited by MILTON L. MCCALL, M.D., F.A.C.S., Professor and Head, Department of Obstetrics and Gynecology, Louisiana State University School of Medicine, New Orleans, etc.; and KARL A. BOLTEN, M.D., Formerly Instructor, Department of Obstetrics and Gynecology, Louisiana State University School of Medicine, New Orleans, etc.; with 450 illustrations by KÄTHE DROYSEN. 405 pages; 26.5 × 18.5 cm. 1957. Little, Brown and Company, Boston. Price, $20.00.

Mental Depressions and Their Treatment. By SAMUEL HENRY KRAINES, M.D., Diplomate American Board of Neurology and Psychiatry, etc. 555 pages; 21 × 14 cm. 1957. The Macmillan Company, New York. Price, $8.00.

Mesenchymal Diseases in Childhood: Report of the Twenty-second Ross Pediatric Conference. 104 pages; 23 × 15 cm. (paper-bound). 1957. Ross Laboratories, Columbus, Ohio. Available on request.

Modern Therapy in Neurology. Edited by FRANCIS M. FORSTER, M.D., Dean and Professor of Neurology, Georgetown University School of Medicine, Washington, D. C.; with foreword by H. HOUSTON MERRITT, M.D., Professor of Neurology, College of Physicians and Surgeons, Columbia University, etc. 792 pages; 22.5 × 14.5 cm. 1957. The C. V. Mosby Company, Saint Louis. Price, $12.00.

Les Nouveaux Syndromes Hémorragiques. La Dysprothrombie: Aspects Actuels—Diagnostic—Traitement. By PAUL CHEVALLIER and A. FIEHRER. 128 pages; 25.5 × 16.5 cm. (paper-bound). 1957. Masson et Cie., Paris. Price, 1.500 fr.

The Practice of Medicine. 6th Ed. Editor: JONATHAN CAMPBELL MEAKINS, C.B.E., M.D., LL.D., D.Sc.; with 24 Associate Editors. 1,916 pages; 26 × 17.5 cm. 1956. The C. V. Mosby Company, Saint Louis. Price, $16.00.

The Principles and Methods of Physical Diagnosis: Correlation of Physical Signs with Certain Physiological and Pathological Changes in Disease. 2nd Ed. By SIMON S. LEOPOLD, M.D., Professor of Clinical Medicine, School of Medicine and Graduate School of Medicine, University of Pennsylvania, etc.; with a chapter on *Sounds from the Thorax: Acoustic Principles* by S. REID WARREN, JR., Sc.D. in E.E., Professor of Electrical Engineering, the Moore School of Electrical Engineering, University of Pennsylvania. 537 pages; 24.5 × 16 cm. 1957. W. B. Saunders Company, Philadelphia. Price, $9.00.

Psychiatric Aspects of School Desegregation. Report 37, formulated by the Committee on Social Issues, Group for the Advancement of Psychiatry. 94 pages; 23 × 15.5 cm. (paper-bound). 1957. Group for the Advancement of Psychiatry, New York. Price, $1.00.

La Puberté: Étude Clinique et Physiopathologique. 2nd Ed. By GUY LAROCHE, A. ASSAILLY, H. BRICAIRE, G. BROUET, E. FERRON, G. HUC, CL. LAROCHE, J. LEPRAT, P. MAURICE, H. SIMONNET, R. TOURNEUR and J. TRÉMOLIÈRES. 395 pages; 25.5 × 16.5 cm. (paper-bound). 1956. Masson et Cie., Paris. Price, 2.800 fr.

Signs and Symptoms: Applied Pathologic Physiology and Clinical Interpretation. 3d Ed. Edited by CYRIL MITCHELL MACBRYDE, A.B., M.D., F.A.C.P., Associate Professor of Clinical Medicine, Washington University School of Medicine, etc. 973 pages; 23.5 × 16 cm. 1957. J. B. Lippincott Company, Philadelphia. Price, $12.00.

Some Milestones in the History of Hematology. By CAMILLE DREYFUS, M.D., Chef de Laboratoire à l'Hôpital St. Antoine, Paris; with a foreword by SIR LIONEL E. H. WHITBY, Regius Professor of Physic, Cambridge University. 87 pages; 23.5 × 15.5 cm. 1957. Grune & Stratton, Inc., New York. Price, $4.50.

Study Group on Paediatric Education: Report. World Health Organization Technical Report Series No. 119. 20 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

A Textbook of Histology. 7th Ed. By ALEXANDER A. MAXIMOW, Late Professor of Anatomy, University of Chicago; and WILLIAM BLOOM, Professor of Anatomy, University of Chicago. 628 pages; 26 × 18 cm. 1957. W. B. Saunders Company, Philadelphia. Price, $11.00.

A Text-book of Surgical Pathology. 7th Ed. By CHARLES F. W. ILLINGWORTH, C.B.E., M.D., Ch.M., F.R.C.S. (Ed.), Regius Professor of Surgery, University of Glasgow; and BRUCE M. DICK, M.B., F.R.C.S. (Ed.), Regional Consultant in Thoracic Surgery, Western Region, Scotland. 730 pages; 24 × 15.5 cm. 1957. Little, Brown and Company, Boston. Price, $14.00.

Therapeutic Exercise for Body Alignment and Function. By MARIAN WILLIAMS, Ph.D., Assistant Professor of Physical Therapy, Department of Allied Medical Sciences, School of Medicine, Stanford University; and CATHERINE WORTHINGHAM, Ph.D., Director of Professional Education, The National Foundation for Infantile Paralysis, Inc.; exercise illustrations by HAROLD BLACK. 127 pages; 27.5 × 21 cm. (loose-leaf). 1957. W. B. Saunders Company, Philadelphia. Price, $3.50.

The Treatment of Burns. By CURTIS P. ARTZ, M.D., F.A.C.S., Lt. Col., MC, USA (Ret.), Formerly, Director, Surgical Research Unit, Brooke Army Medical Center, Fort Sam Houston, Texas, etc.; and ERIC REISS, M.D., American Cancer Society Scholar and Instructor in Medicine, Washington University School of Medicine, St. Louis, Missouri; illustrations by BURR BUSH. 250 pages; 25.5 × 16.5 cm. 1957. W. B. Saunders Company, Philadelphia. Price, $7.50.

Vegetable Oils in Nutrition, With Special Reference to Unsaturated Fatty Acids. By DOROTHY M. RATHMANN, Ph.D., Multiple Fellowship of Corn Products Refining Company, Mellon Institute, Pittsburgh. 70 pages; 21.5 × 15.5 cm. 1957. Corn Products Refining Company, New York. Available on request.

Your Wonderful Body. By PETER PINEO CHASE, M.D. 391 pages; 23.5 × 16 cm. 1957. Prentice-Hall, Inc., Englewood Cliffs, New Jersey. Price, $5.95.